Combining Brachytherapy and Cryotherapy as Adjuvant Therapy for Squamous Cell Carcinoma of the Conjunctiva: Literature Review and Case Reports

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Keywords

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results by combining the 2 adjuvant therapies showing no signs of recurrence or complications during a follow-up period of 26 and 38 months.

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Abstract

Background: Separately, cryotherapy and brachytherapy have shown promising results when adjuvating the excision of squamous cell carcinoma of the conjunctiva (SCCC). The aim of this paper is to assess the combined effect in terms of complications and recurrence rate. **Summary:** We describe 2 patients suffering from SCCC, and we review the current literature on adjuvant cryotherapy and brachytherapy. Both patients, one of whom suffered from recurrent SCCC, underwent surgical excision followed by combined cryotherapy and brachytherapy. Cryotherapy was performed using a retinal cryoprobe, and 2 rounds each of 5 s with N₂O as a cryogen were applied. Brachytherapy was performed using a ruthenium-106 plaque, delivering a dosage of 100 Gy at 2-mm depth. **Key Messages:** By reviewing the current literature and describing 2 case reports, this paper illustrates the use of combined cryotherapy and brachytherapy after surgical excision of SCCC. The current literature presents promising results of each treatment, and the 2 cases showed promising

Introduction

Squamous cell carcinoma of the conjunctiva (SCCC) is the most common conjunctival malignancy in the world. As the incidence of SCCC declines by 49% for each 10° increase in latitude [1], the isolated incidence rate is 0.02 per 100,000 men and 0.008 per 100,000 women per year in Denmark (55–57° north), correlating well with other studies in northern, high-latitude areas [2].

At such latitudes, SCCC is primarily found in Caucasian men above 60 years of age, located at the nasal or temporal conjunctiva in the interpalpebral region close to the limbus. The most characteristic clinical appearance is a nonpigmented, irregularly shaped growth, with a thickness above 1 mm with feeder and/or intrinsic vessels [3].

Disease control of up to 100% has been reported when SCCC is treated using excision with clear surgical margins, while the recurrence rate with residual tumor cells

of the margins may be as high as 53% [4]. When adjuvant surgical excision of SCCC with cryotherapy, reported recurrence rates vary from 0 to 50% [5–10]. Brachytherapy is also used as adjuvant therapy of excision, resulting in recurrence rates of 0–20% [11–19].

This paper reviews the literature on adjuvant cryotherapy and brachytherapy to assess the combined effect, which could result in further reduction of recurrence rates. Two case reports are described, in one of which the patient suffered from recurrent SCCC. Both cases were treated with excision adjuvated by combined cryotherapy and brachytherapy using 2 rounds of 5 s with N₂O as a cryogen and a 15.3-mm ruthenium-106 (Ru-106) plaque, due to the recurrent disease (pt. 1) or large tumor size (pt. 2). No complications or recurrences were observed during follow-up periods of 26 and 38 months.

Methods

This study includes 2 patients suffering from bulbar SCCC. Both patients were treated with surgical excision followed by adjuvant cryo- and brachytherapy at our institution in the years 2016–2019. Written informed consent to publish clinical photographs was obtained from both patients.

A PubMed search was performed on English publications, using the terms “squamous cell carcinoma,” “conjunctival cancer,” “corneal cancer,” “conjunctival tumor,” “corneal tumor,” “squamous neoplasia,” “squamous cell neoplasia,” “SCCC,” “plaque therapy,” “brachytherapy*,” “surface radiotherapy,” “conjunctiva*,” “cornea*,” “orbital*,” and “ophthalmological*.” Furthermore, the abovementioned terms were combined using the MeSH terms “conjunctival neoplasms” and “brachytherapy.” The resulting articles were reviewed for similar articles. When relevant studies were found, a manual search of references was conducted. Studies were excluded if data on SCCC in terms of recurrence rates and complications were not specified.

Case Presentations

Case 1

An 88-year-old male presented with a greyish, elevated tumor located temporally in the left conjunctiva covering part of the cornea (shown in Fig. 1). The patient had undergone bilateral cataract surgery at the age of 82, but the visual acuity of the left eye after cataract surgery was only 0.17 due to epiretinal fibrosis.

At presentation, visual acuity measured 1/60 on the left eye compared to 6/12 on the right eye. A squamous cell carcinoma at the same location had been excised 3 years prior without adjuvant therapy.

Before surgery, photo documentation was performed, while neither optical coherence tomography (OCT) or ultrasound biomicroscopy (UBM) was performed. The excision of the recurrent lesion comprised alcohol-assisted epitheliectomy and release of the tumor from the cornea followed by sharp excision of the conjunctival tumor, stopping at bare sclera.

The conjunctival surgical margin was marked using bipolar diathermia aiming at a 3-mm margin to the tumor. Lamellar scleral excision was not performed, though advised by authorities [20]. Frozen sections of the conjunctival margins and scleral base were not performed. The tumor was easily released from its scleral base, showing no signs of scleral invasion.

Cryotherapy of the conjunctival margins was performed using a retinal cryoprobe, and 2 rounds of freezing each of 5 s with N₂O as a cryogen were performed. After cryotherapy, a Ru-106 plaque was sutured over the tumor site for a total of 28 h, resulting in a calculated tissue deposit of 100 Gy at 2-mm depth and a maximum dose of 237 Gy at the scleral bed. The use of brachytherapy was based on the recurrence of SCCC.

Histopathological examination showed a polypoid process consisting of pleomorphic and hyperplastic squamous tumor cells with several atypical mitoses. The tumor was well differentiated with intercellular bridges and keratinization and invaded the underlying inflamed stroma. The diagnosis of SCCC was confirmed by immunohistochemistry using anti-cytokeratin (CK) 5 and anti-p40. The human papillomavirus (HPV) surrogate marker p16 and HPV DNA polymerase chain reaction (PCR) were both negative. The surgical margins could not be evaluated. Clinical examination 26 months later showed no evidence of recurrence, and the visual acuity of the left eye was 0.5/60.

Case 2

A 64-year-old male presented with a pale, solid tumor at the temporal corneal limbus with moderate ciliary injection (shown in Fig. 2). The tumor measured 6.5 × 5.5 mm. One month prior, the patient started experiencing irritation with redness laterally in the right eye. A week later, the patient noticed a rapidly growing tumor. Visual acuity measured 6/10 on the left eye and 6/6 on the right.

Before surgery, photo documentation was performed, while neither OCT or UBM was executed. The excision comprised alcohol-assisted epitheliectomy and release of the tumor from the cornea followed by sharp excision of the conjunctival tumor, stopping at bare sclera.

Fig. 1. Squamous cell carcinoma of the conjunctiva treated with excision, cryotherapy, and a ruthenium plaque. **a** An 88-year-old male presented with a tumor located to the temporal corneal limbus. **b** Excisional biopsy was performed followed by cryotherapy and suture of a ruthenium plaque over the tumor bed. The plaque was removed after 100 Gy had been delivered at 2-mm depth. **c** At 4 months, the eye was almost calm, with no sign of early recurrence.

Fig. 2. Squamous cell carcinoma of the conjunctiva treated with excision, cryotherapy, and a ruthenium plaque. **a** A 64-year-old male presented with a temporally located tumor on the right eye just crossing the limbus with ciliary injection. **b** Excisional biopsy was performed followed by cryotherapy and suture of a ruthenium plaque over the tumor bed. The plaque was removed after 100 Gy had been delivered at 2-mm depth. **c** At 3-year follow-up, there had been no sign of recurrence.

The conjunctival surgical margin was marked using bipolar diathermia aiming at a 3-mm margin to the tumor. Lamellar scleral excision was not performed, though advised by authorities [20]. Frozen sections of conjunctival margins and scleral base were not performed. The tumor was easily released from its scleral base, showing no signs of scleral invasion.

Cryotherapy of the conjunctival margins was performed using a retinal cryoprobe, and 2 rounds of freezing each of 5 s with N_2O as a cryogen were performed.

After cryotherapy, a Ru-106 plaque was sutured over the tumor site for a total of 19 h, resulting in a calculated tissue deposit of 100 Gy at 2-mm depth and a maximum dose of 239 Gy at the scleral bed. The use of brachytherapy was based on the size of the tumor.

Histopathological examination showed a tumor composed of well-differentiated, squamous tumor cells. Infiltrative islands were seen in the underlying desmoplastic stroma. There were multiple squamous eddies and atypical mitoses present in the tumor tissue. By immunohisto-

Table 1. Literature review (1989–2020) reporting the use of cryotherapy as adjuvant treatment when excising squamous cell carcinoma of the conjunctiva

Author country	N	Histology	Cryotherapy (cryogen)	Median age, years	LR, n (%)	LR of SCCC, n (%)	Primary % of LR SCCC, n (%)	Salvage % of LR SCCC, n (%)	Mean follow-up, months	Complications
Peksayar et al. [7] Turkey	22	12 SCCC 10 CIN	+ Margins + Scleral bed (N ₂ O)	59.7	2 (9)	2 (16.7)	1 (50)	1 (50)	72	5 minimum corneal scarring 2 sectoral iris atrophy 2 temporary ocular hypertension 1 temporary ocular hypotension 1 corneal hemorrhage 1 superficial corneal vascularization
Tunc et al. [10] USA	60	38 SCCC* 22 CIN	+ Margins + Scleral bed (NR)	64	3 (5)	2* (8.3)	Nil	2 (100)	56	4 mild symblepharon 2 graft contractions 2 pannus 1 dellen 1 corneal scarring 1 hypertropia 1 descemetocoele 1 astigmatism
Sudesh et al. [9] USA	28	18 CIS 7 D 2 SCCC 1 AK	+ Margins – Scleral bed (N ₂ O)	66	5 (17.9)	1 (50)	Nil	1 (100)	38	Nil
Sturges et al. [8] USA	14	10 CIN 4 SCCC	+ Margins – Scleral bed (NR)	63.9 ^m	Nil	Nil	Nil	Nil	35.6	Nil
Palamar et al. [6] Turkey	21	10 SCCC 9 CIN 2 D	+ Margins – Scleral bed (NR)	62.4 ^m	Nil	Nil	Nil	Nil	30.9	3 partial limbal stem cell deficiency 1 symblepharon
Li et al. [5] USA	43	24 CIS 14 D 5 SCCC	+ Margins – Scleral bed (NR)	69	3 (7)	Nil	Nil	Nil	29 ^{md}	NR
Current study (2020) Denmark	2	2 SCCC	+ Margins – Scleral bed (N ₂ O)	76	Nil	Nil	Nil	Nil	26–38	Nil
N	190	59 SCCC		–	13/190 (6.8)	5/59 (8.5)	1/5 (20)	4/5 (80)	–	–

^m, mean; ^{md}, median; n, number of cases; LR, local recurrence; Primary, first treatment; Salvage, recurrent treatment; SCCC, squamous cell carcinoma of the conjunctiva; CIN, conjunctival intraepithelial neoplasia; D, dysplasia; AK, actinic keratosis; CIS, carcinoma in situ; NR, not reported. * 24 of 38 SCCC patients received adjuvant cryotherapy.

chemistry, the tumor cells were positive in pan-CK and negative in Melan-A, confirming the diagnosis of SCCC. The surgical margins could not be evaluated. Two months later, visual acuity of both eyes measured 6/6. Follow-up after 38 months showed no evidence of recurrence.

Discussion

We describe 2 cases of SCCC in the limbal region, one of which suffered from recurrent SCCC. Both cases presented with characteristic clinical findings. Both patients were Caucasian males above 60 years of age and had tumors located at the temporal conjunctiva of the interpalpebral region in proximity of the limbus. Both tumors appeared nonpigmented with an irregular growth, vessel formation, and a papilliform surface.

The 2 cases were successfully treated with excision adjuvated by cryotherapy and plaque brachytherapy using a

106-ruthenium plaque. In both cases, the adjuvant effect of combining cryo- and brachytherapy controlled the site of concern, effectively delivering its radioactive dose in 28 and 19 h, respectively. We used Ru-106 plaques due to its frequent use when treating ocular malignant melanomas, thus making it the available type of brachytherapy in our institution.

Surgical excision of SCCC is usually combined with adjuvating therapies such as cryotherapy, topical mitomycin C, topical 5-fluorouracil, or interferon- $\alpha 2\beta$ [21]. Furthermore, several radiotherapeutic treatments have been suggested, including brachytherapy [22].

Adjuvant Cryotherapy

Adjuvating the excision of SCCC with double freeze-thaw cryotherapy to the surgical margins is considered the gold standard [20] and probably the most commonly used adjuvant treatment of SCCC (Table 1) [5–10]. However, some studies [7, 10] also include the scleral base when adjuvating surgical excision with cryotherapy. The

adjunctive effect of cryotherapy is due to obliteration of the microcirculation, which leads to ischemic infarction of the surrounding tissue [23, 24].

The literature describes 59 cases of SCCC treated with surgical excision followed by adjuvant cryotherapy. Of those 59 SCCC cases, 5 recurred during variable follow-up periods, resulting in an average recurrence rate of SCCC managed by excision adjuvated by cryotherapy of 8.5% (Table 1). Reports of local recurrence range from 0 to 16.7% in most cases, while Sudesh et al. [9] reported recurrence in 1 of 2 salvaged SCCC patients (50%). The percentage of reported SCCC recurrences relies heavily upon whether patients underwent primary (20%) or salvage treatment (80%), highlighting the importance of lowering the primary recurrence rate as much as possible in the first place, in order to reduce the need for salvage treatment.

Several studies report the potential complications of cryotherapy, presenting as corneal inflammation and scarring, symblepharon, pannus formation, sectoral iris atrophy, corneal hemorrhage, descemetocoele, and astigmatism [6, 7, 10]. If cryotherapy is extensively used near the limbus, it may lead to limbal stem cell insufficiency [25], as observed by Palamar et al. [6]. In our 2 cases, no complications of cryotherapy were reported within the follow-up periods, possibly because cryotherapy was applied only to the conjunctival margins and not to the sclera or cornea.

Adjuvant Brachytherapy

When treating SCCC with excision, brachytherapy is also used as an adjuvant therapy. After excision of conjunctival or corneal tumors, the tumor bed can be treated using a number of radioactive sources such as strontium-90 (Sr-90), iodine-125 (I-125), or ruthenium-106 (Ru-106) [22]. Other radiotherapeutic options, such as electron- and proton-beam radiotherapy, have also shown promising results, with reported disease control in up to 100% of cases [14, 26–28].

Ru-106 is a beta emitter with a half-life of 374 days. With a tissue penetration (half-value layer [HVL] = 2.4 mm) in between those of Sr-90 (HVL = 1.5 mm) and I-125 (HVL = 20 mm), the useful range of Ru-106 is 5–6 mm, compared to 2 mm for Sr-90 and 13 mm for I-125 [22]. When using Sr-90, the radioactive dose is delivered by a handheld device, while both Ru-106 and I-125 are sutured to the ocular surface, allowing a more precise plaque localization [19]. Because the radioactive isotope in the standard Ru-106 and I-125 plaques is attached to the concave surface of the plaque, the use of such plaques is limited to bulbar malignancies and can-

not be used for SCCC located in the fornices or in the tarsal conjunctiva.

The specific usage of Ru-106 brachytherapy has previously been reported by Zehetmayer et al. [19] in 1993 as well as Kenawy et al. [14] in 2015. Zehetmayer et al. [19] described 2 cases, one of which suffered from SCCC. With a dosage of 240 Gy at 1 mm, they had no sign of recurrence in 22 months but did report scleral rarefaction as a complication. Kenawy et al. [14] opted for 100 Gy at 1 mm for both primary and salvage SCCC. In a total of 19 cases, they reported no recurrences or long-term ocular complications at follow-up medians of 69 months (primary group) and 55 months (salvage group).

Based on these limited data, it seems reasonable to assume that a higher dosage of radiation increases the risk of radiotherapeutic complications. While the literature on Ru-106 brachytherapy is scarce, there seems to be a consensus in the effectiveness of brachytherapy in general. The available literature on the treatment of SCCC is based on case series, leaving an optimal line of treatment undetermined, since no comparative studies exist.

The literature describes 116 cases of SCCC treated with surgical excision followed by adjuvant brachytherapy. Of those 116 SCCC cases, 7 recurred during variable follow-up periods, resulting in an average recurrence rate of SCCC managed by excision adjuvated by brachytherapy of 6.0% (Table 2) [11–19]. Most studies report recurrence rates of 0–14.8%, while Laskar et al. [15] reported recurrence in 2 of 10 SCCC patients (20%).

Complications of brachytherapy are well known, presenting as radiation conjunctivitis, dry eye, uveitis, cataract, scarring, symblepharon, ulceration, scleral or corneal thinning, corneal perforation, keratopathy, glaucoma, and retinopathy [16, 18, 29]. In our case series, no complications due to brachytherapy were reported.

Since the lens is the most radiosensitive structure of the eye, cataract presents as one of the most common complications of brachytherapy [11]. However, both cataract and glaucoma seem to occur more often in older individuals receiving brachytherapy. In 2015, Lecuona et al. [16] had no reports of cataract in their 69 cases, which correlates well with the low median age of 42 years in their series.

In general, the use of plaque radiotherapy provides a very focused radioactive deposit on targeted tissue, minimizing the irradiation of surrounding and deeper tissue. It also eliminates the dependency of patient compliance, as is the case with other adjunctive treatments such as topical chemotherapy. However, sizing the plaque correctly is paramount in terms of recurrence. In 2015, Lecuona et al. [16] noted the importance of plaque sizing in

Table 2. Literature review (1976–2020) reporting the use of brachytherapy as adjuvant treatment of squamous cell carcinoma of the conjunctiva

Author country	N	Histology	Median age	Emitter	Dose	Total LR, n (%)	SCCC LR, n (%)	Median follow-up, months	Complications
Lommatsch [17] Germany	15	10 SCCC 4 CIN 1 EP	64.2	Strontium-90/ yttrium-90	100–180 Gy	1 (6.7)	Nil	12–96	X transitory irritation 3 corneal scarring 1 cataract 1 triangular opacity 1 partial symblepharon 1 secondary glaucoma
Kearsley et al. [13] Australia	140	78 CIS 62 SCCC	56	Strontium-90 ^a	31 Gy ^m	3 (2.4) ^a	NR	97	X transitory irritation 3 telangiectasia 2 scleral defects 2 cataract
Cerezo et al. [12] Spain	27	15 IE 12 SCCC	63	Strontium-90	60 Gy ^{SDT} 140 Gy ^{Fr}	4 (14.8)	1 (8.3)	24–180	X transitory irritation 5 cataract
Zehetmayer et al. [19] Austria	2	1 CM 1 SCCC	72.5 ^m	Ruthenium-106	CM 200 Gy SCC 240 Gy	Nil	Nil	36 ^m	X scleral rarefaction
Walsh-Conway et al. [18] Australia	11	5 CM 6 SCCC	60.8	Iodine-125	100 Gy	Nil	Nil	23.4	5 corneal ulceration 4 reduced peripheral corneal vascularization
Arepalli et al. [11] USA	15	15 SCCC	70	Iodine-125	56 Gy apex ^m 95 Gy base ^m	Nil	Nil	42	13 cataract 5 telangiectasia 4 corneal defect 3 corneal edema 1 glaucoma
Kenawy et al. [14] UK	41	Primary treatment: 9 SCCC 11 CIS Salvage treatment: 10 SCCC 11 CIS	62 63	Ruthenium-106	100 Gy	3 (7.3)	Nil	Primary: 69 Salvage: 54.5	Nil
Laskar et al. [15] India	13	10 SCCC 1 MGC 1 BK 1 MALT-L	47	Strontium-90	30–50 Gy ^{Fr}	2 (20)	2 (20)	51	4 telangiectasia 1 limbal scar 1 limbal opacification
Lecuona et al. [16] South Africa	69	41 SCCC 28 CIS	42	Strontium-90	60 Gy ^{Fr}	8 (11.6)	4 (9.8)	27	5 dry eye 1 astigmatism
Current study (2020) Denmark	2	2 SCCC	76 ^m	Ruthenium-106	100 Gy	Nil	Nil	26–38	Nil
N	335	116 SCCC ^b	–	–	–	21/335 = 6.3%	7/116 = 6.0%	–	–

^m, mean; ^{md}, median; ^{SDT}, single-dose treatment; ^{Fr}, fractionation; X, unnumbered; n, number of cases; SCCC, squamous cell carcinoma of the conjunctiva; CIN, conjunctival intraepithelial neoplasia; EP, epidermalization; CIS, carcinoma in situ; CM, conjunctival melanoma; IE, intraepithelial epithelioma; MGC, meibomian gland carcinoma; BK, Bowenoid keratosis; MALT-L, mucosa-associated lymphoid tissue lymphoma; LR, local recurrence; SDT, single-dose treatment. ^a 123 of 140 patients were treated using strontium-90. ^b Excluding Kearsley et al. [13] due to lack of specifics on SCCC LR.

relation to recurrence rates, finding recurrence rates of 0% when using 18-mm plaques and 16.3% when using 8.5-mm plaques. Recurrences were caused by edge-recurrence due to a smaller active field of radiation.

Combining Adjuvant Cryotherapy and Brachytherapy

Separately, the use of adjuvant cryotherapy and adjuvant brachytherapy lowers the recurrence rate of SCCC. The goal of combining them is to further increase their potency while keeping complications at a minimum.

The amount of literature on the combined use of cryotherapy and brachytherapy in an adjuvant setting is extremely limited, even though both modalities are widely available and commonly used. Of the 9 reviewed studies listed in Table 2, only Arepalli et al. [11] and the present

study used a combination of the 2 therapies. In the study by Arepalli et al. [11], the choice of combination was based on histopathological confirmation of invasion of the sclera and/or anterior chamber after initial treatment of excisional biopsy, superficial keratectomy, and conjunctival cryotherapy. Their choice of emitter was I-125, delivering a mean apex dose of 56 Gy and a mean base dose of 95 Gy for a mean duration of 132 h. Radiation-induced complications were numerous, including cataract, telangiectasia, epithelial defects, corneal edema, and glaucoma (Table 1). However, of the 15 cases treated, no local recurrences were reported. It is worth noting that most of the cases were referred due to recurrence of SCCC ($n = 10$), making the local recurrence rate of 0% even more prominent.

In our study, the decision of combining adjuvant cryotherapy and brachytherapy was based on the recurrent disease of case 1 and the tumor size of case 2. When combining therapies in this manner, it is crucial to consider the fact that the patients are subjected to the complications of both treatments, which must be outweighed by the reduction of recurrences. In our 2 cases, no complications or recurrences were reported after combining surgical excision with adjuvant cryotherapy and brachytherapy within follow-up periods of 26 and 38 months.

Conclusion

The combined effect of adjuvant cryotherapy and brachytherapy is difficult to determine from the literature due to the rare occurrence of SCCC. Adding the lack of consensus regarding treatment regimens and adjuvant modalities makes it even more difficult to determine the combined effect [30].

Opting for a combined adjuvant therapy may lower the recurrence rate of SCCC. However, this advantage must be weighed against a possible increase in severe complications from subjecting the patients to both cryotherapy and brachytherapy.

While our study is not sufficiently powered to draw any conclusions, it is our hope that the presented cases increase the awareness of combining adjuvant cryotherapy and brachytherapy for bulbar SCCC and that they result in further studies of the combined effect of adjuvant therapies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.S.F. (Bachelor of Medicine) wrote the manuscript, receiving substantial contribution from I.M.S.R. (medical doctor) and P.B.T. (medical doctor, Doctor of Medical Science) on the acquisition of cases as well as analysis and data interpretation of the work. P.S.F., I.M.S.R., and P.B.T. critically revised the drafts, approved the final version before publication, and agreed on accountability regarding the accuracy and integrity of the finished product.

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