Plaque Radiotherapy in the Management of Scleral-Invasive Conjunctival Squamous Cell Carcinoma
An Analysis of 15 Eyes

Sruthi Arepalli, BA; Swathi Kaliki, MD; Carol L. Shields, MD; Jacqueline Emrich, PhD; Lydia Komarnicky, MD; Jerry A. Shields, MD

IMPORTANCE Conjunctival squamous cell carcinoma (SCC) is surgically managed with wide surgical excisional biopsy, superficial keratectomy, and cryotherapy. In eyes with residual tumor showing scleral invasion or intraocular involvement, enucleation is advised.

OBJECTIVE To explore the role of plaque radiotherapy for residual invasive conjunctival SCC as an alternative to enucleation.

DESIGN, SETTING, AND PARTICIPANTS Interventional case series involving 15 patients with histopathologically confirmed scleral and/or intraocular invasion of SCC at Wills Eye Hospital.

INTERVENTION Plaque radiotherapy.

MAIN OUTCOMES AND MEASURES Tumor control, treatment complications, and globe salvage.

RESULTS The primary tumor prior to excision displayed a mean basal diameter of 12.1 mm (median, 12 mm; range, 4-25 mm) and mean thickness of 2.6 mm (median, 3 mm; range, 1-5 mm). In all cases, the tumor was managed by primary surgical resection using wide excisional biopsy, limited superficial keratectomy, and cryotherapy to the remaining conjunctival margins. Histopathology confirmed conjunctival SCC in all cases with residual tumor demonstrating scleral invasion (n = 15) and/or anterior chamber invasion (n = 3). The residual tumor measured a mean basal diameter of 10.6 mm (median, 10 mm; range, 2.5-20 mm) and mean thickness of 1.5 mm (median, 1 mm; range, 1-5 mm). Plaque radiotherapy was applied in all cases for a mean apex dose of 56 Gy (median, 50 Gy; range, 50-80 Gy) over a mean of 132 hours (median, 142 hours; range, 93-170 hours). Over a mean follow-up of 41 months (median, 46 months; range, 9-96 months), local tumor control was achieved in all 15 cases (100%). However, 4 cases showed further distant conjunctival tumor recurrence remote from the site of radiotherapy with positive orbital involvement at a mean of 5 months postradiotherapy, necessitating enucleation (n = 2) or orbital exenteration (n = 2). Globe salvage was achieved in 10 cases, as 1 patient required enucleation for chronic ocular irritation. Radiation complications included cataract (n = 13), iris telangiectasia (n = 5), corneal epithelial defect (n = 4), corneal edema (n = 3), and glaucoma (n = 1). There was no evidence of metastasis.

CONCLUSIONS AND RELEVANCE Plaque radiotherapy delivered over a mean of 6 days can be an effective alternative to enucleation for residual scleral-invasive conjunctival SCC following resection. Local tumor control was achieved in all cases.

Published online February 20, 2014.

Copyright 2014 American Medical Association. All rights reserved.
Conjunctival squamous cell carcinoma (SCC) is a neo-
plastic process with anaplastic cells originating in the
surface epithelium invading deep to the basement
membrane into the conjunctival stroma.\(^1\)\(^-\)\(^7\) This condition classi-
cally arises in elderly patients in the sun-exposed region of
the conjunctiva. In an analysis of 1643 patients with conjunc-
tival tumors, SCC represented 108 (7%) of all cases.\(^5\) In that
analysis, the median patient age at presentation was 69 years
and this tumor predominated in white individuals (90%) com-
pared with African American (6%), Hispanic (4%), and Asian
(<3%) individuals.\(^5\)

Conjunctival SCC generally involves the limbal region and
can display various configurations, including sessile, papillo-
matous, or a nodular appearance, and can show features of pig-
mentation and leukoplakia.\(^1\)\(^-\)\(^4\) This malignancy usually re-
 mains on the surface of the globe, but intraocular invasion is
found in 3% to 9% of cases and orbital invasion in 1% to 6%.\(^5\)\(^-\)\(^10\)
Mucoepidermoid and spindle cell carcinoma, both aggres-
sive forms of SCC, are particularly prone to scleral or intraocu-
lar invasion.\(^11\)\(^-\)\(^13\) Metastases are notably rare.\(^1\)

Conjunctival SCC management depends on tumor loca-
tion and size and usually involves excisional biopsy, alcohol-
treated limited superficial keratectomy, and conjunctival cryo-
 therapy, using the no-touch technique.\(^14\)\(^-\)\(^18\) Topical medica-
tions can be useful for primary or secondary treatment of conjunc-
tival SCC using mitomycin C (MMC), 5-fluorouracil, and inter-
feron alfa-2b.\(^5\)\(^-\)\(^10\)\(^-\)\(^24\) However, when conjunctival SCC invades
deep into the sclera or into the globe, topical medications are
ineffective and enucleation is often necessary.\(^2\) In this re-
port, we explored an alternative to enucleation using plaque
radiotherapy for invasive conjunctival SCC.

Methods

This retrospective interventional case series included pa-
 tients with SCC managed with wide excisional biopsy of tu-
mor, superficial keratectomy, and conjunctival cryotherapy
who were found on clinical and histopathology examination
to have scleral or anterior chamber invasion. In each case,
plaque radiotherapy was applied at the Ocular Oncology Ser-
dvice, Wills Eye Hospital, Philadelphia, Pennsylvania, in con-
junction with the Department of Radiation Oncology, Drexel
University College of Medicine, Philadelphia, Pennsylvania,bet-
ween October 1999 and September 2007. Institutional re-
view board approval was obtained at Wills Eye Hospital, and
written informed consent was obtained from patients.

Patient data were extracted from medical records and in-
cluded patient age at diagnosis (years), sex (male or female),
race/ethnicity (white, African American, Hispanic, or Asian),
presenting symptoms, carcinomas elsewhere in the body, au-
toimmune disease, immunosuppression (organ transplant,
HIV/AIDS, oral steroids, or topical steroids), prior ocular treat-
ment, and lymph node involvement (submandibular, ante-
rior cervical, or preauricular). The ocular features included best-
corrected visual acuity (VA), intraocular pressure (mm Hg),
tumor laterality (unilateral or bilateral), configuration (nodu-
lar, flat, papillomatous, or sessile), tumor multiplicity (unifo-
cal or multifocal), tumor basal dimensions and thickness (mil-
limeters), corneal involvement, number of quadrants involved
by tumor, quadrant containing the epicenter of tumor (super-
ior, inferior, nasal, and temporal), leukoplakia, presence of in-
trinsic blood vessels, intraocular involvement (anterior cham-
ber, iris, ciliary body, and choroid), and associated ocular
findings (pinguecula, pterygium, cataract, and actinic kerato-
sis). The tumor basal diameter and thickness were measured
with slitlamp biomicroscopy and confirmed with ultrasound
biomicroscopy (UBM). All findings were documented with large
color anterior drawing, slitlamp photography, anterior-
segment optical coherence tomography, and UBM. Histopatho-
logic diagnosis of invasive SCC was confirmed in all cases.

The potential risks and benefits of plaque radiotherapy
were discussed with the patient, and written informed con-
sent was obtained. Each tumor was treated with a custom-
designed iodine-125 (I125) plaque to cover the residual inva-
sive tumor with a surrounding 2-mm margin. Initial
follow-up examination was performed 1 to 4 months after
plaque removal. Features recorded at each follow-up visit
included best-corrected VA, tumor response (including
basal diameter and thickness, measured by both slitlamp
biomicroscopy and UBM), status of tumor, recurrence, com-
plications from treatment, and globe salvage. Visual acuity
at each follow-up visit was compared with initial best-
corrected VA and categorized as stable, improved (increase
in vision by ≥2 Snellen lines), or decreased (decrease in
vision by ≥2 Snellen lines). Patient outcome (alive, alive
with metastasis, death due to metastasis, or death due to
other causes) was noted.

Results

Patient demographic information is listed in Table 1. The mean
patient age was 70 years (median, 71 years; range, 50-83 years).
The most common presenting sign was a painless mass (n = 6).
Three patients had coexistent SCC/actinic keratosis of the face.

Squamous cell carcinoma features before surgical exci-
sion and the residual invasive tumor features before plaque ap-
lication are listed in Table 2. Before excision, at the date of
presentation, the mean tumor basal diameter was 12.1 mm (me-
dian, 12 mm; range, 4-25 mm), and mean thickness was 2.6 mm
(median, 3 mm; range, 1-5 mm). The tumor involved tempo-
ral (n = 9) or nasal (n = 6) quadrants. Corneal involvement
was found in 11 cases, for a mean of 3.5 clock hours (median, 3 clock
hours; range, 2-9 clock hours). While 13 patients were man-
aged with a variety of treatments prior to referral, all patients
with active primary tumor (n = 2) and recurrent tumor (n = 10)
were treated with excisional biopsy, superficial alcohol kera-
tectomy, and cryotherapy at Wills Eye Hospital (n = 12). Three
patients had undergone excisional biopsy, alcohol keratec-
tomy, and cryotherapy elsewhere and were referred to us for
microscopic residual disease.

Following excision, histopathology revealed carcinoma in-
volve ment of deep margins into sclera in all cases. In 3 cases,
anterior chamber involvement was clinically detected and con-
firmed with UBM (Table 3).
Plaque radiotherapy was applied in all cases. The features immediately prior to plaque radiotherapy are listed here. The mean residual tumor basal diameter measured 10.6 mm (median, 10 mm; range, 2.5-20 mm) and the mean thickness was 1.5 mm (median, 1 mm; range, 1-5 mm). Plaque radiotherapy was applied for a mean duration of 133 hours (median, 142 hours; range, 93-170 hours) with a mean apex dose of 56 Gy (median, 50 Gy; range, 50-80 Gy) and a mean base dose of 95 Gy (median, 67 Gy; range, 45-285 Gy). Radiotherapy dosage was determined by the head radiation oncologist. Because this was a retrospective study (more than 8 years), 2 main oncologists determined the plaque dosage, with one preferring 80 cGy and another preferring closer to 50 cGy. The mean time duration between excisional biopsy and plaque radiotherapy was 2 months (median, 1 month; range, 0-5 months).

Table 1. Demographics of 15 Patients Who Had Plaque Radiotherapy in the Management of Scleral-Invasive Conjunctival SCC

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Patients (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (median) [range], y</td>
<td>70 (71) [50-83]</td>
</tr>
<tr>
<td>White</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Eye involved</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Left</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Systemic disease</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression due to CLL</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Facial skin malignancies</td>
<td></td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>1 (7)</td>
</tr>
<tr>
<td>SCC</td>
<td>2 (13)</td>
</tr>
<tr>
<td>No. of treatments before referral</td>
<td></td>
</tr>
<tr>
<td>Mean (median) [range]</td>
<td>2 (2) [0-5]</td>
</tr>
<tr>
<td>Patients with treatment before referral</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Topical antibiotics</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Incisional biopsy</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Excisional biopsy</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Excisional biopsy and cryotherapy</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Topical steroid</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Topical interferon alpha-2b</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
</tr>
<tr>
<td>Painless mass</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Redness</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Tearing</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Decreased vision</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; SCC, squamous cell carcinoma.

Table 2. Tumor Features Before Excision and Before Plaque Radiotherapy in the Management of Scleral-Invasive Conjunctival SCC in 15 Eyes

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Patients (N = 15 Tumors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tumors per eye (N = 15 eyes)</td>
<td></td>
</tr>
<tr>
<td>Mean (median) [range]</td>
<td>3.5 (3) [2-9]</td>
</tr>
<tr>
<td>Solitary</td>
<td>12 (12) [4-5]</td>
</tr>
<tr>
<td>Multiple</td>
<td>2.6 (3) [1-5]</td>
</tr>
<tr>
<td>Location of tumor epicenter</td>
<td></td>
</tr>
<tr>
<td>Limbus</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Bulbar conjunctiva</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Plica semilunaris</td>
<td>1 (7)</td>
</tr>
<tr>
<td>No. of clock hours of corneal involvement</td>
<td></td>
</tr>
<tr>
<td>Mean (median) [range]</td>
<td>6.1 (6) [5-9]</td>
</tr>
<tr>
<td>Tumor basal dimension, mm</td>
<td>12.6 (12) [4-5]</td>
</tr>
<tr>
<td>Tumor thickness, mm</td>
<td>2.6 (3) [1-5]</td>
</tr>
<tr>
<td>Tumor configuration</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Sessile</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Flat</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Papilliform</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Associated features</td>
<td></td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Intrinsic blood vessels</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Feeder vessels</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Intraocular involvement</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Anterior chamber</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Abbreviation: SCC, squamous cell carcinoma.

The plaque was applied directly to the sclera (n = 7) or on the surface of the conjunctiva if lateral margins were histopathologically positive (n = 8).

Following plaque radiotherapy, radiation complications included cataract (n = 13), iris telangiectasia (n = 5), corneal epithelial defect (n = 4), corneal edema (n = 3), and glaucoma (n = 1). These were unrelated to plaque dosage. One patient had...
chronic ocular irritation and nonhealing corneal epithelial irregularity that required enucleation. The VA remained stable in 4 eyes and decreased in 11 eyes owing to cataractal eyes and glaucoma in the patient with vision decreased to no light perception.

At mean follow-up of 42 months (median, 46 months; range, 7-96 months), local tumor control was achieved in all 15 cases (100%). However, further tumor recurrence at a distant conjunctival site remote from the radiotherapy and within the globe was detected in 4 cases at a mean follow-up of 5 months postplaque (median, 5 months; range, 1-8 months), with no relationship to plaque dosage. The patients with further remote recurrence had aggressive disease and/or immune incompetence with bilateral involvement (n = 2), coexistent chronic lymphocytic leukemia (n = 1), or immunosuppression for lupus erythematosis (n = 1). Treatment for remote recurrence included orbital exenteration (n = 2) or enucleation (n = 2). Overall, of the 15 irradiated eyes, globe salvage was achieved in 10 cases (67%). Of the 3 eyes with initial anterior chamber tumor invasion, tumor control was achieved in 2 cases and globe salvage in 1 case (Table 3).

Discussion

Traditionally, alcohol keratectomy and wide excisional biopsy with cryotherapy is the most common treatment for invasive SCC.1-4,9,14,15 Tumor involvement of margins represents a major risk factor for recurrence.9 Recurrence following surgical excision alone has been published to occur in approximately 30% of cases, and as high as 69% in those with documented positive surgical margins, while recurrence following wide excisional biopsy combined with cryotherapy are fairly low at 8% to 16%.9,16-18 Advanced SCC can invade into the eye through the sclera or cornea or invade into the soft tissues of the orbit.10,15 In such cases, enucleation or orbital exenteration is often used.4

In recent years, topical chemotherapeutic agents, such as MMC and 5-fluorouracil, have shown efficacy in the control of widespread or multifocal conjunctival SCC, occasionally with local corneal toxicity. Topical or injection interferon alfa-2b has been proven safe and effective for extensive, recurrent, or bilateral conjunctival SCC, with minimal toxicity. However, these agents do not normally penetrate the sclera or into the eye, thus render-
Plaque Radiotherapy for Conjunctival SCC

For these reasons, we explored the role of plaque radiotherapy for control of conjunctival SCC with scleral or intraocular invasion. Plaque radiotherapy has been previously used to control residual microscopic tumor following surgical resection of conjunctival SCC. Initial reports on beta radiation using strontium-90 revealed nearly 100% success rates in cases of superficial conjunctival SCC. Similar results have been observed with ruthenium-106. Beta radiation provides precise, low-penetration radiotherapy with sharp margins but has the limitation of short depth of field.

Gamma radiotherapy using I125 has also been explored as an adjunctive treatment to excision for invasive conjunctival SCC because it has a deeper penetrability compared with beta radiation. Walsh-Conway and Conway treated 6 patients with scleral-invasive conjunctival SCC with I125 radiotherapy. During a mean follow-up period of 23 months, 1 episode of distant conjunctival recurrence developed.

In our analysis of 15 patients with conjunctival SCC demonstrating scleral invasion in every case and intraocular invasion in 3 cases, plaque radiotherapy, with a gamma source of I125, provided satisfactory local tumor control in every case (Figure 1). Nearly all of our cases had previous therapy elsewhere with 1 or more recurrences following excisional biopsy (n = 8; 53%), excisional biopsy and cryotherapy (n = 5; 33%), and/or topical MMC/interferon alfa-2b (n = 5; 33%). These challenging cases were referred with the understanding that they might need major surgery or enucleation/exenteration. In every case, I125 plaque radiotherapy controlled the site of concern, but in 4 cases, further remote tumor progression within the eye and/or orbit led to the need for enucleation (n = 2) or exenteration (n = 2). Underlying factors of immune suppression, found in 2 cases, could have played a role in these cases with progressive recurrence.

Plaque radiotherapy provides precise, targeted therapy to affected structures with decreasing dose to immediately surrounding tissues and relatively low dose to more remote normal tissue. The tumor dimensions are important in plaque configuration and seed orientation (Figure 2). In our cases, the plaque size varied from 13 mm to 22 mm in diameter. In most cases, the plaque was sutured directly to the sclera to treat scleral invasion, but in 3 cases, the plaque was sutured over the cornea to cover the entire residual scleral-invasive tumor for 2-mm depth.
effectively delivered over a mean of 6 days. Temporary Gundersen flap and suture tarsorrhaphy provided comfort.

In our series, radiation complications reflected the anterior plaque location, particularly for those with anterior chamber invasion. Complications included cataract in 13 cases, transient corneal epithelial defect in 4, iris telangiectasia in 5, corneal edema in 3, and glaucoma in 1. The lens is the most radiosensitive structure in the eye and shows damage with dosages less than 1 Gy. Management of the radiotherapy effects included cataract extraction \( n = 2 \). Of the 4 patients with corneal epithelial defect, 3 had previously received MMC, which could have contributed to surface epithelial incompetence. Of the 5 cases of iris telangiectasia postradiotherapy, none progressed to neovascularization or glaucoma. Of the 3 cases of corneal edema, partial resolution occurred in 1 and persistent edema remained in 2. Corneal graft was not performed.

Conclusions

Plaque radiotherapy is a safe and reliable alternative to globe removal for eyes with conjunctival SCC demonstrating scleral invasion and/or intraocular involvement. Precise radiotherapeutic isodose design and plaque placement are critical in aligning the focal radiation field appropriately. Affected eyes should be followed up for remote recurrence at other sites.

ARTICLE INFORMATION

Submitted for Publication: June 22, 2013; final revision received October 3, 2013; accepted October 16, 2013.

Published Online: February 20, 2014. doi:10.1001/jamaophthalmol.2014.86.

Author Contributions: Dr C. L. Shields had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Arepalli, Kaliki, C. L. Shields, J. A. Shields.

Acquisition of data: Arepalli, Emmrich, J. A. Shields.

Analysis and interpretation of data: Arepalli, Emmrich, Komarnicky.

Drafting of the manuscript: Arepalli, C. L. Shields.

Critical revision of the manuscript for important intellectual content: Kaliki, C. L. Shields, Emmrich, Komarnicky, J. A. Shields.

Statistical analysis: Arepalli, C. L. Shields.

Administrative, technical, and material support: C. L. Shields, Emmrich, Komarnicky, J. A. Shields.

Study supervision: Kaliki, C. L. Shields, J. A. Shields.

Conflict of Interest Disclosures: None reported.

Funding/Support: Support for this study was provided by the Eye Tumor Research Foundation, Philadelphia, Pennsylvania (Drs C. L. Shields and J. A. Shields), and for A Cure for A Cure, Morrisdale, Pennsylvania (Dr C. L. Shields).

Role of the Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES


