Intraepithelial and invasive squamous cell carcinoma of the conjunctiva: analysis of 60 cases

Murat Tunc, Devon H Char, Brooks Crawford, Theodore Miller

Abstract

Aim—To evaluate the clinical features, treatment results, and recurrence rates in patients with either intraepithelial or invasive squamous cell carcinoma of the conjunctiva.

Methods—Retrospective analysis of 60 cases (22 conjunctival intraepithelial and 38 invasive squamous cell carcinomas) to determine patterns of clinical presentation, aetiological factors, and treatment results. The mean patient age was 64 years old. 70% of the patients were male. Patients were treated with a variety of therapies, depending on the degree of tumour involvement; most cases were treated with frozen section controlled excision and adjunctive cryotherapy. Modified eye wall resection or enucleation was done for intraocular invasion and exenteration was done for orbital involvement.

Results—Red eye (68%) and ocular irritation (57%) were the most common presenting symptoms. 44% of the patients had other eye findings consistent with extensive solar exposure. 20% of the patients had a history of malignant skin tumours. Visceral malignancies developed in 8%. Scleral involvement was present in 14 (37%), intraocular involvement in five (13%), and orbital invasion in four (11%) cases with invasive squamous cell carcinoma. After a mean follow up of 56 months (18–226 months) the rate of new or recurrent tumours was 4.5% for intraepithelial squamous carcinoma and 5.3% for invasive squamous cell carcinoma. No patient developed metastases or tumour related deaths.

Conclusion—Excision with intraoperative control of the surgical margins and adjunctive cryotherapy results in good tumour control rates.

Conjunctival squamous cell carcinoma (intraepithelial and invasive) is the most common conjunctival malignancy in the United States. The incidence of this neoplasm is between 1 and 2.8 per 100 000 people per year and varies in different geographic locations. Epidemiological studies have shown that ultraviolet B radiation (290–320 nm) may be important in its pathophysiology. Ultraviolet B induced point mutations in the p53 tumour suppressor gene have been reported in other squamous cell carcinomas. Human papillomavirus (HPV) types 16 and 18 may also be important in tumour development.

Intraepithelial squamous carcinoma (also known as conjunctival intraepithelial neoplasia, or conjunctival intraepithelial neoplasia, previously known as Bowen’s disease) and invasive squamous cell carcinoma of the conjunctiva are histologically differentiated according to the invasion of epithelial basement membrane. In invasive squamous cell carcinoma cells infiltrate through the basement membrane and invade the substantia propria. Although intraepithelial squamous carcinoma may progress to invasive squamous cell carcinoma, the former lesions are localised in the epithelium.

Clinically these tumours most commonly arise in the interpalpebral area of the perlimbal conjunctiva. The growth may be in a nodular, gelatinous, flat superficial leucoplakic, or diffuse invasive fashion. These tumours may present as localised slowly growing lesions that mimic benign conjunctival degenerations and sometimes coexist with pinguecula and pterygia. Diffuse tumours in older patients may be misdiagnosed as a chronic unilateral conjunctivitis. Bowman’s layer usually is a barrier to invasive disease. Rarely the initial lesion appears on palpebral conjunctiva. Long term neglected invasive lesions may spread into the globe or orbit.

The treatment options for conjunctival epithelial malignancies include tumour removal with or without cryotherapy, radiotherapy and topical chemotherapy. The reported incidence of recurrence after initial treatment is quite variable. Previous reports reveal high recurrence rates after simple surgical excision. Invasive disease may cause intraocular and orbital involvement with eye loss.

In order to evaluate the clinical features, recurrence rates, and the outcome of treatment modalities we performed a retrospective analysis of our cases.

Patients and methods

Sixty eyes of 59 patients with pathological confirmation of either intraepithelial or invasive squamous cell carcinoma were included in this study. These patients were managed by one of us (DHC) between 1977 and 1996. Benign conjunctival tumours and other types and variants of conjunctival malignancies were excluded. Patients with less than 18 months of follow up were also excluded from this analysis. Forty patients, referred either for initial treatment or after an outside biopsy, showed tumour at the resection margins. Nineteen
Conjunctival squamous cell neoplasia
99
and eight of 37 (22%) squamous cell carcinoma. Two patients with intraepi-
thelial tumours (9%) and three patients with invasive squamous cell carcinoma (8%) devel-
oped visceral malignancies after the diagnosis of the conjunctival tumour. Two patients had
colon carcinomas, and the three other patients each developed lung, breast, and renal cell car-
nomas. None of these patients with a second visceral malignancy had a known cancer diathesis.

The conjunctival lesion was located on the temporal limbal conjunctiva in 50% of cases.
Thirteen cases (59%) with intraepithelial neo-
plasia and 21 cases (55%) with invasive carcinoma had corneal involvement. Intraepi-
thelial tumours had a limbal involvement of
less than three clock hours in 18 (82%), three
to six clock hours in three (14%), and more
than six clock hours in one (4%) case. In inva-
sive squamous cell carcinoma, limbal involve-
ment was less than three clock hours in 23
(61%), between three and six clock hours in 10
(26%), and more than six clock hours in five
(13%) cases.

Intraepithelial squamous carcinoma lesions
were nodular gelatinous (elevated, focal masses
with a vascular, mulberry appearance) in
11 (50%), flat leucoplakic in nine (41%), and
superficial diffuse in two (9%) cases. The clini-
cal appearance of invasive squamous cell carci-
noma lesions were nodular gelatinous in 16
(42%), flat, localised leucoplakic in six (16%),
and diffuse infiltrative in 16 (42%) cases. The
lesion had intrinsic tumour and/or feeder
vessels in 14 cases (64%) with intraepithelial
tumours, and in 25 cases (66%) with invasive
squamous cell carcinoma. Secondary pigmen-
tary changes were present in two intraepithelial
and one invasive squamous cell carcinoma
lesions.

We primarily managed 14 of 22 intraepithe-
lial squamous carcinoma cases; eight patients
were referred because of recurrences after
initial treatment elsewhere. Initial treatment
modalities are summarised in Table 1. In all
cases we performed excision with frozen
section control and adjunctive cryotherapy. In
one of eight cases referred for recurrence, a
second recurrence developed 14 months later

### Results

Histopathologically there were 22 intraepi-
thelial tumours and 38 invasive squamous cell
carcinomas. The right eye was involved in 27
patients, and left in 31. Squamous cell carcinoma of the conjunctiva was bilateral in
one patient. The patients were between 26 and
84 years old with a mean age of 64 years old.
There was a male predominance (41 men and
18 women). Fifty three patients were white,
four were Hispanic, and two were Asian. Most
of the patients were retired at the time of diag-
nosis; 14 had a previous outdoor and 45 an
indoor occupation.

The most common presenting symptoms
were red eye in 41 (68%) and ocular irritation
in 34 (57%) patients. Other complaints such as
decreased vision, itching, and photophobia
were also present in six patients. Two patients
had no complaints and the lesion was detected
during a routine eye examination. Almost half
the patients (26 of 59) had another ocular
finding associated with extensive sun exposure
such as pterygium, pinguecula, solar elastosis,
or nuclear sclerosis.

Four of 22 (18%) intraepithelial neoplasia
and eight of 37 (22%) squamous cell carci-
noma patients had a history of a malignant
cutaneous tumour. Eleven were basal cell
carcinomas and one was a cutaneous epider-
moid carcinoma. Two patients with intraepi-
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### Table 1 Initial diagnosis and management of the patients

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>Initial treatment centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN† SCC† UCSD‡ Others</td>
<td></td>
</tr>
<tr>
<td>E+TCA</td>
<td>0 2 2 0</td>
</tr>
<tr>
<td>E+C+L</td>
<td>0 4 4 0</td>
</tr>
<tr>
<td>E+RT</td>
<td>0 4 0 4</td>
</tr>
<tr>
<td>E+TCA</td>
<td>0 2 0 2</td>
</tr>
<tr>
<td>EN</td>
<td>0 1 1 0</td>
</tr>
<tr>
<td>E+L</td>
<td>0 2 0 2</td>
</tr>
<tr>
<td>Total</td>
<td>22 38 40 20</td>
</tr>
</tbody>
</table>

*E=total excision; C=cryotherapy; LKS=lamellar keratolamellar
rectomy; LT=limbal transplantation; RT=radiotherapy; TCA=topical
cytotoxic agents; EN=enucleation; EXE=enukleation.
†CIN=conjunctival intraepithelial neoplasia; SCC=squamous
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such as pterygium, pinguecula, solar elastosis,
or nuclear sclerosis.

Four of 22 (18%) intraepithelial neoplasia
and eight of 37 (22%) squamous cell carci-
Symblepharon was mild and did not require secondary repair in three of the cases.

Pannus or corneal scar was out of visual axis and did not require additional treatment.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cases (n)</th>
<th>Postoperative complications</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision + cryotherapy</td>
<td>27</td>
<td>Pannus*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dellen</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corneal scar formation*</td>
<td>1</td>
</tr>
<tr>
<td>Excision + cryotherapy +</td>
<td>14</td>
<td>Hypertropia</td>
<td>1</td>
</tr>
<tr>
<td>lamellar sclerectomy</td>
<td></td>
<td>Descemetocele</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astigmatism</td>
<td>1</td>
</tr>
<tr>
<td>Excision + cryotherapy +</td>
<td>8</td>
<td>Contraction of the graft</td>
<td>2</td>
</tr>
<tr>
<td>free mucosal grafts</td>
<td></td>
<td>Symblepharon†</td>
<td>4</td>
</tr>
</tbody>
</table>

*Pannus or corneal scar was out of visual axis and did not require additional treatment.
†Symblepharon was mild and did not require secondary repair in three of the cases.

and required retreatment. After a mean follow up of 56 months (18–223 months) the overall recurrence rate was one in 22 (4.5%) for intraepithelial tumours. The last post-treatment visual acuity was better than 20/40 in 18 of 22, and better than 20/60 in the remaining four patients.

We performed initial therapy on 27 of the 38 conjunctival invasive squamous cell carcinoma cases; treatment modalities are summarised in Table 1. Scleral involvement was present in 14 (37%) of 38 invasive cases. Five patients (13%) had intraocular involvement of the anterior chamber angle. Four (11%) cases had orbital involvement at the time of the referral.

Eleven cases were referred with recurrent tumours. Five of the recurrent cases had previous surgical excision, four had excision and radiotherapy, and two had prior excision with adjunctive topical cytotoxic therapy. The mean interval between the initial management and the diagnosis of recurrence was 18 months. In patients referred with recurrent disease we performed excision with frozen section control and adjunctive cryotherapy in five patients; four of these also had lamellar keratosclerectomy with scleral and/or limbal grafts. In the other six cases with more extensive tumours, two each had enucleation, exenteration, and modified eye wall resection.

Two of the invasive squamous cell carcinoma cases we initially managed developed recurrences. Both of these patients had been referred to us with positive tumour margins. We had initially managed these cases with frozen section controlled excision and cryotherapy. The second case was more extensive and also required a lamellar keratosclerectomy. Both of these cases underwent a second excision with intraoperative control of surgical margins and adjunctive cryotherapy. Neither has recurred within a follow up of 48 months.

None of the cases recurred after eye wall resection, enucleation, or exenteration. Our overall recurrence rate for conjunctival squamous cell carcinoma was two of 38 (5.3%), with a mean follow up of 55 months (18–226 months). In both recurrent cases we obtained tumour control. No patients developed metastatic disease or were lost to follow up.

Visual results of invasive conjunctival carcinoma were related to the tumour extent and other ocular disease. The last visual acuity was better than 20/40 in 18 of 22 and between 20/40 and 20/80 in six cases who retained their eyes. In two of six cases in the latter group decreased vision was secondary to the tumour or the treatment. In two patients, the vision was less than 20/100 because of an age related cataract or aphakic bullous keratopathy. Seven eyes were lost due to intraocular or orbital invasion. One referred case had lost his vision due to previous radiotherapy and we performed an enucleation, as the eye was blind and painful.

After surgical removal and cryotherapy, pannus formation developed in two cases; in neither case did this cause visual loss. Eight cases were treated with mucosal grafts and minor degrees of symblepharon developed in four; one case required repair. In one case we resected the insertion of the inferior rectus because of tumour invasion. This case developed hypertropia and required a secondary muscle surgery. Surgical complications are summarised in Table 2.

### Discussion

Conjunctival epithelial malignancies are more common in elderly and male patients, but may develop at a younger age especially in association with xeroderma pigmentosum or immunodeficiency. None of our cases had these latter predisposing factors. Some reports have noted a younger age in intraepithelial cases compared with invasive squamous cell carcinoma, but we did not observe this in our series. In line with previous reports we noted a male predominance probably due to increased occupational exposure to sunlight.

In almost half of our patients other solar eye changes were noted.

Cutaneous and visceral malignancies in association with conjunctival epithelial tumours have been reported. Some investigators no longer use this terminology. Visceral malignancies were noted in five (8%) of our cases, in agreement with other reports. In an epidemiological investigation of uveal melanoma patients, we noted that over 10% had another malignancy. In that analysis we noted that this was not significantly above age matched controls and the mean age was similar in conjunctival malignancies.

The importance of HPV types 16 and 18 in the pathophysiology of conjunctival carcinoma is uncertain. Some previous reports indicate the association of human papillomavirus 16 (HPV-16) with some cases of bilateral conjunctival dysplasia. In some studies as many as 77% of cases have had immunohistochemical evidence of these viruses. Other authors have noted HPV in a number of non-malignant solar related conjunctival lesions. We did not perform a controlled study of HPV in our patients’ tumours.

Conjunctival squamous cell neoplasms are more frequent in immunocompromised patients. It was estimated that the relative
risk of conjunctival epithelial malignancies increased 13-fold in patients with acquired immune deficiency syndrome (AIDS).

Some investigators have suggested that as many as 50% of patients, less than 50 years old, with conjunctival neoplasia may have AIDS. None of our younger patients had a history of, or developed, immune deficiency. While we are surprised by the lack of AIDS patients in our study cohort, it may reflect referral bias, false negative diagnosis, or other unknown factors.

Squamous cell carcinoma of the palpebral conjunctiva is uncommon; misdiagnosis often reflects a tertiary referral practice. Deep corneal delays treatment and increases morbidity. Intraocular invasion may also reflect regional lymph nodes. Intraocular invasion has been reported in over half of our cases. In cases that involved the cornea we removed the involved epithelium with a scalpel; others have reported the use of alcohol or excimer laser. Bowman’s layer is usually a natural barrier and if possible should be left intact; deeper keratectomy and extensive cryotherapy may cause corneal scar formation, dellen, and astigmatism.

Scleral involvement is a risk factor for both tumour recurrence and intraocular invasion. Described scleral involvement in 21% of cases and it was present in 14 (37%) of our invasive cases. It is difficult to accurately delineate the deep tumour margins with a very small piece of tissue that has been further reduced in size to determine the tumour status of its horizontal edges. Given the histological sampling limits with conjunctival tumours, we routinely treat the scleral base and conjunctival margins with double freeze cryotherapy. Most cases referred to us with recurrent tumour had previous excisions without cryotherapy.

Intraocular invasion has been reported between 2% and 8% of cases. We noted a slightly higher incidence (13%), probably reflecting a tertiary referral practice. Deep corneal stromal invasion and involvement of anterior chamber structures suggest intraocular invasion.

Intraocular invasion may also present with iritis, glaucoma, retinal detachment, or rupture of the globe. Gonioscopy should be performed in all cases to determine whether diffuse peripheral anterior synechiae are present which are a hallmark of intraocular invasion. A tumour with small localised intraocular invasion without diffuse anterior chamber seeding may be successfully treated with a modified eye wall resection.

Previous studies reported orbital invasion in 12–16% of invasive cases. We noted a similar incidence and anterior orbital exenteration was necessary in all of them. Local invasion is the most prevalent mechanism of tumour spread. Metastases are rare, and the first site of extraocular involvement is regional lymph nodes. Radiation and topical cytotoxic agents have been used to treat some conjunctival carcinomas.

Radiotherapy and topical cytotoxic agents were used to treat some conjunctival carcinomas. Kearns and associates reported 140 invasive cases treated with strontium-90 radiotherapy with a recurrence rate of 2.3%. Complications after strontium-90 irradiation include scleral necrosis and cataract formation; external beam radiation may produce a dry painful eye and visual loss due to radiation vasculopathy. In our series three patients were referred after radiation treatment failures. Radiation has a limited role in the management of this neoplasm. Our control rate with surgery has been excellent. In diffuse tumours, radiation can destroy the reproductive integrity of the malignancy, but radiation damage may result in a staged anterior exenteration.

There are limited data on topical cytotoxic therapy. Frucht-Pery and Rozenman reported six conjunctival intraepithelial neoplasia cases with topical 5-fluorouracil; five responded well but one progressed and required exenteration. Good short term conjunctival intraepithelial neoplasia response has been reported after topical 0.04% mitomycin therapy. In our series two eyes with squamous cell carcinoma were treated elsewhere with excision and topical cytotoxic agents for about 1 month (5-fluorouracil and cyclosporin A) and recurred in 12–18 months. In a comprehensive published series there is a paucity of long term follow up with topical mitomycin. A few intraepithelial and invasive cases have failed and a study of more patients with longer follow up is needed. Since local failures, as discussed below, have had a mean time to recurrence between 8 and 22 months, the long term efficacy of topical agents is uncertain.

Surgical complications include corneal scarring, symblepharon, ocular hypotony, and iris atrophy. Most cases referred to us by corneal specialists had large diffuse tumours. As a result, we required larger buccal as opposed to conjunctival autologous grafts. Our most common surgical complication was symblepharon; only one case required secondary symblepharon correction. In contrast with some reports, we did not observe hypotony after double freeze thaw cryotherapy.

Visual results after our treatment were excellent. Only two cases with squamous cell carcinoma had low vision (<20/60) due to tumour or treatment. Previous reports demonstrate that if the tumour involves more than 40% of the cornea, excision combined with adjunctive cryotherapy resulted in persistent corneal inflammation, intrastral neovascularisation, and poor vision. In such cases limbal grafts improved epithelial healing and prevented ocular surface problems.

Recurrence of conjunctival epithelial malignancies depends on the status of surgical margins. Simple excision of conjunctival intraepithelial or invasive neoplasia is associated with a 24–50% recurrence rate. Several histological features are important for tumour recurrence; however, even in cases with milder degrees of atypia, careful assessment of histological margins is mandated. Tabin and associates excised intraepithelial tumours without intraoperative control of surgical
margins; 25% had positive margins and incompletely excised cases developed twice as many recurrences as those with tumour free margins.22 We controlled the surgical margins by frozen sections and applied adjunctive cryotherapy. Our recurrence rates, 4.5% for intraepithelial tumours and 5.3% for squamous cell carcinoma, are lower than most of the previous reports.1,17,21–31 Ernie and associates32 reported a recurrence rate of 41% in squamous cell carcinoma and 23.5% in conjunctival intraepithelial neoplasia after local excision with a follow up of 6 months to 39 years. Irvine33 reported a 10% local recurrence rate but half of the cases had either no, or less than 1 year, of follow up. Follow up examinations for longer than 12 months are necessary as the mean time to recurrence has been reported between 8 and 22 months.1,17,21–31 Buuns and associates34 reported no recurrence in 19 squamous cell carcinoma cases with microscopically controlled excision, a modification of Mohs’ micrographic surgery, but some of these cases had only 6 months of follow up and four of 19 required a second operation.

Conjunctival squamous cell neoplasms can cause significant ocular morbidity. Early diagnosis and intervention can prevent major eye damage. Surgery with control of margins and adjunctive cryotherapy has a very high success rate. Technical modifications may further reduce ocular damage, although more long term follow up is necessary to determine the optimal role for some of these newer treatment options.


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