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CLINICAL STUDY

An audit of conjunctival melanoma treatment in Liverpool

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Abstract

Purpose **To evaluate treatment of conjunctival melanomas at the Ocular Oncology Service in Liverpool.**
Methods **We included 40 patients initially treated at our centre for invasive conjunctival melanoma and 36 patients referred for salvage therapy after surgery elsewhere. Patients underwent local excision or radiotherapy. Adjunctive cryotherapy for invasive and intra-epithelial neoplasia was abandoned in favour of ruthenium brachytherapy and mitomycin C chemotherapy, respectively. Tumours were staged according to circumferential spread, basal diameter, and histological thickness.**
Results **The 40 previously-untreated tumours were confined to bulbar conjunctiva in 31 patients and involved extrabulbar conjunctiva in 9, affecting caruncle in 6 of these. All eyes were conserved, most retaining initial visual acuity. Invasive conjunctival recurrence, which occurred in six patients, was more likely with medial tumours (Log-rank, $P = 0.004$) and if treatment did not include radiotherapy (Log-rank, $P = 0.03$). Four patients died of metastases, all with caruncular involvement. Of the 36 patients referred for salvage therapy after previous surgery, 11 had no visible tumour, 9 had only intra-epithelial neoplasia, and 16 had invasive melanoma, which was recurrent in seven. After salvage therapy, five patients died, all of whom were referred with recurrent invasive tumour and only one of whom had caruncular involvement.**
Conclusions **Excision of invasive melanoma with adjunctive brachytherapy and topical chemotherapy achieved high rates of local tumour control with little ocular morbidity. Without caruncular involvement, disease-specific mortality was rare unless the patient was referred after a surgical procedure. Our results suggest that inadequate surgical intervention increases risks of local recurrence and metastatic death.**

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Keywords: melanoma; conjunctival neoplasms; disease-specific mortality; ophthalmology; pathology; treatment

Introduction

Invasive conjunctival melanoma accounts for only 1–2% of all ocular melanomas.[1] About 50% of tumours are associated with diffuse intra-epithelial melanocytic neoplasia, consisting of pre-existing 'primary acquired melanosis (PAM) with atypia' (which we prefer to call 'conjunctival *in situ* melanoma') (Damato and Coupland, Clinical Experimental Ophthalmology, submitted) and/or secondary pagetoid spread from the invasive tumour.[2]

Previously, many patients with conjunctival melanoma underwent orbital exenteration.[3,4] Local excision with adjunctive radiotherapy or radiotherapy alone was reported by Treacher Collins in 1917 and by others but has not gained widespread acceptance.[5–13] Cryotherapy was popularised by Jakobiec in the 1980s and still has its advocates.[14–16] Treatment with a topical caustic agent was reported in 1893.[17] Topical chemotherapy with mitomycin C was introduced in the 1990s.[18,19]

Local recurrence is common, with some studies reporting rates exceeding 50%.[15,20,21] Tumours can spread to regional lymph nodes and metastasise systemically.[22] The 10-year melanoma-related mortality is approximately 25–30%.[15,20,21,23] Risk factors for metastasis include non-bulbar conjunctival involvement,

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diffuse intra-epithelial disease, local tumour recurrence, multifocal tumours, increased tumour thickness, high mitotic rate, epithelioid cells, and lymphatic invasion.[24–27]

Much of the published evidence relating to conjunctival melanomas and their treatment is not relevant to current patients because of recent therapeutic advances and because tumour staging at initial presentation has not been well reported. Furthermore, several studies are confusing because they include patients initially treated at a non-specialist centre so that tumour staging and management may have been suboptimal.

We have recently developed a system for mapping conjunctival tumours, which has improved our ability to define the location and extent of invasive and intra-epithelial melanoma.[2]

The aim of this study was to audit the treatment of conjunctival melanomas at the Ocular Oncology Service in Liverpool, according to whether or not initial surgery was performed at our centre and with initial tumour status defined using our mapping system.

Patients and methods

Patients were included in this study if treated for histologically confirmed conjunctival melanoma at our centre between January 1993 and December 2006. Those referred for salvage therapy after biopsy or excision elsewhere were studied separately. Two patients initially treated elsewhere were excluded from this audit because their notes were no longer available.

Visual acuity was measured with a Snellen chart until January 2006 and with a LogMAR chart since then. Full ocular examination was performed in the standard manner, together with inspection of the superior tarsal conjunctiva and fornix with a magnifying lens, gently pulling the eyelid away from the eye, hence avoiding painful, double-eversion of the eyelid. Regional lymph nodes were palpated routinely.

The patients were identified by searching the computerised database of the Liverpool Ocular Oncology Centre and archives of the Pathology Department at the Royal Liverpool University Hospital. All casenotes, computerised records, histological sections, and clinical photographs were reviewed to define tumour location and extent. If not documented in the casenotes at the time of initial assessment, measurements such as basal dimensions and distances from limbus and lid margin were made from photographs. Calibration for such measurements was based on corneal diameter. Tumour thickness was determined histologically. Perpendicular sections of the excised conjunctival melanomas were stained with haematoxylin and eosin and immunohistochemically using a melanocytic marker, MelanA. The deepest point of infiltration was measured in micrometres on orthograde sections using a digital image analysis system (Olympus Soft Imaging Solutions GmbH, Munster, Germany). Invasive melanoma and intra-epithelial neoplasia were mapped both numerically and using a conjunctival diagram, according to circumferential spread in clock minutes in cornea, limbus, bulbar conjunctiva, fornix, palpebral conjunctiva, lid margin, and eyelid skin, with specific mention of plica or caruncle involvement (Figure 1).[2]

Tumours were staged according to the 6th edition of the Tumour Node Metastasis (TNM) system.[28] Briefly, this categorises the primary tumour as TI if limited to the bulbar conjunctiva; TII if the cornea is affected; TIII if the tumour involves non-bulbar conjunctiva (ie, fornix or palpebral conjunctiva) and TIV if there is spread of tumour into globe, eyelid skin, orbit, nasal sinuses, or intra-cranial cavity (Table 1).

Treatment consisted of excision of any tumour nodules, performing corneal epithelial debridement with alcohol and a Bard Parker knife, using a no-touch technique, applying bipolar diathermy for haemostasis and to any visible deep extension of tumour, using fresh instruments for wound closure. Amniotic membrane grafting was not required in any patient. Any deep invasion demonstrated histologically was treated with liquid nitrogen cryotherapy until 1997 when it was superseded by brachytherapy. This was administered using a 15 mm ruthenium-106 plaque delivering a dose of 100 Gy to 2 mm, this dose being reduced in 2006 to 100 Gy at 1 mm. The plaque was sutured to the limbus by its two lugs and a mattress suture was used to ensure good apposition. Towards the end of this study, we used a bandage contact lens to minimise discomfort. Intra-epithelial neoplasia was treated with liquid nitrogen cryotherapy until 1999, when this treatment was replaced by topical chemotherapy using mitomycin C drops, four times daily for a total of 4 weeks, initially in two 14-day cycles, separated by a 2-week interval, and latterly in four 7-day cycles over 8 weeks. In 2006, the concentration of mitomycin C was reduced from 0.04 to 0.02% to reduce toxicity. Punctal occlusion was not performed in case the melanoma had seeded into the nasolacrimal duct. After tumour excision, any brachytherapy or mitomycin C treatment was delayed for 3 or 4 weeks until the conjunctival wound had healed. For the purposes of this audit, any cryotherapy, brachytherapy, or mitomycin C treatment was considered as adjunctive therapy, if administered within 100 days of the initial local tumour excision. In the early years, most patients had multiple microbiopsies every 6–12 months, but after we started using topical chemotherapy, we performed such biopsies only if there were any suspicious areas of pigmentation.

Ocular follow-up was measured to the last known ocular status, as determined by assessment at our centre

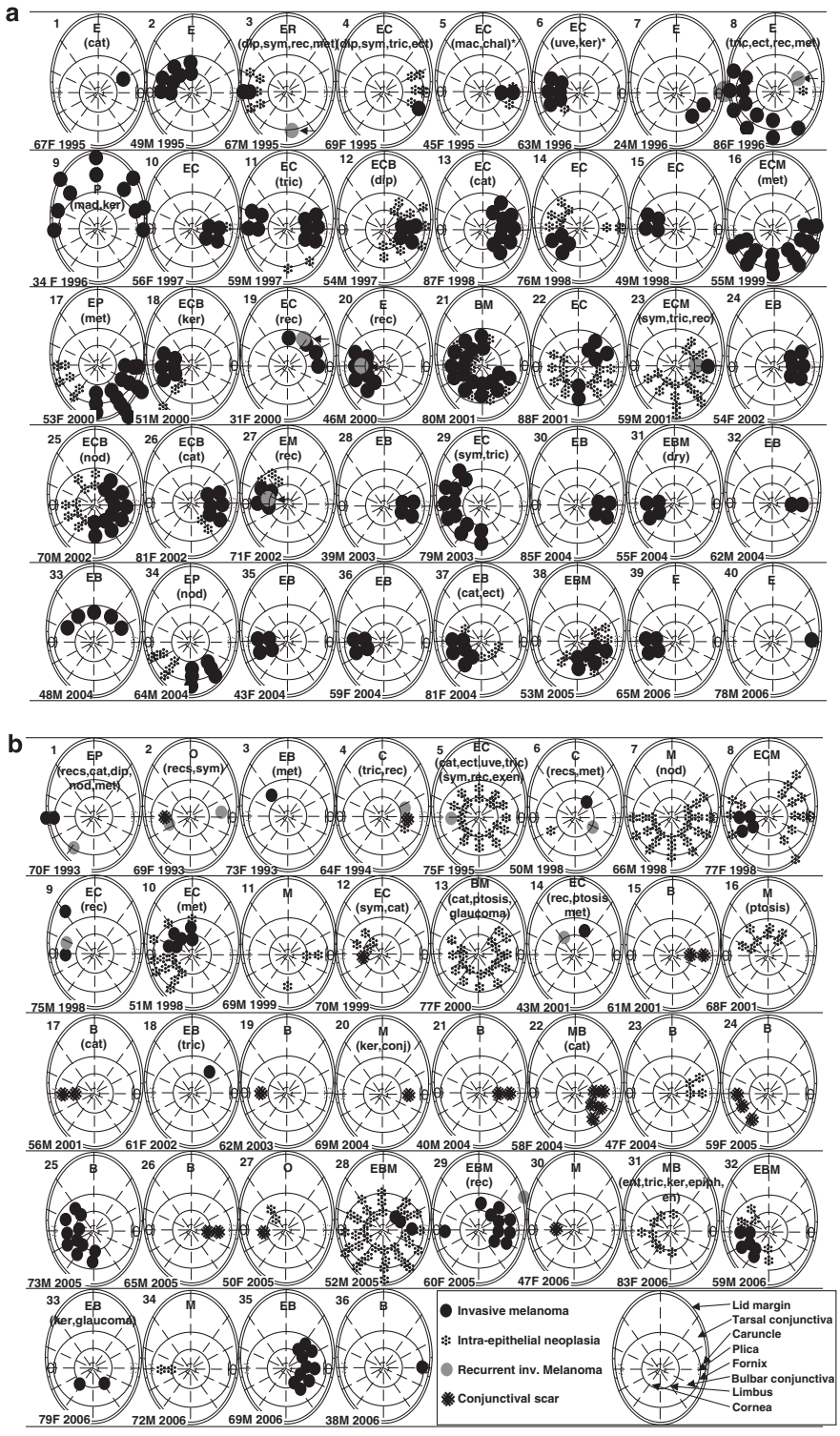

Figure 1 Maps of (a) 40 conjunctival melanomas first treated at our centre, and (b) 36 eyes referred after treatment of conjunctival melanoma elsewhere.[2] These show location and extent of disease. Each spot represents involvement of a sector of conjunctiva and not a separate tumour. See side of caruncle to determine whether left or right eye is involved. (E = Excision, C = cryotherapy, B = brachytherapy, P = proton beam radiotherapy, M = mitomycin C treatment, cat = cataract, dip = diplopia, uve = uveitis, ker = keratopathy, mac = macular oedema, mad = madarosis, sym = symblepharon, tric = trichiasis, ect = ectropion, dry = dry eye, chal = chalazion, rec = recurrence, nod = nodal metastasis, met = metastatic death).

Table 1 Proposed staging system for conjunctival melanoma

Current 6th edition of TNM staging	*Our proposed system*[a]
No *in situ* melanoma	Tis: *in situ* melanoma a: Bulbar, less than 1 quadrant b: Bulbar, $>=1$ quadrant c: Non-bulbar d: Involvement of eyelid skin.
TI: Bulbar conjunctiva No sub-categorization according to size or quadrant	TI: Bulbar conjunctiva a: Less than 1 quadrant b: 1–2 quadrants c: >2 quadrants d: Intraocular invasion
TII: Corneal involvement Unsubstantiated assumption that corneal involvement aggravates prognosis	TII: Palpebral conjunctiva without caruncular involvement a: Less than 1 quadrant b: 1–2 quadrants c: >2 quadrants d: Eyelid skin involvement
TIII: Non-bulbar conjunctiva No categorization according to tumour size. No consideration of quadrant or caruncular involvement.	TIII: Palpebral conjunctiva with caruncular involvement a: Less than 1 quadrant b: 1–2 quadrants c: >2 quadrants d: Invasion of lacrimal sac.
TIV: Eyelid, intraocular, orbital, sinusal or intracranial spread No distinction between different levels of risk (eg, eyelid and intracranial spread considered equal)	TIV: Orbit, sinus or intracranial invasion a: Superficial orbit (ie, to equator of globe) b: Deep orbit (ie, retro-ocular) c: Nasal sinuses d: Intracranial cavity

[a]This proposal has been recently submitted to the present TNM/AJCC staging committee and is currently being reviewed.

or follow-up information obtained from referring ophthalmologists. Survival time was measured to the date of death or to 15 June 2007, if the patient was alive at this date. With patients resident in mainland Britain, this was confirmed with the NHS Cancer Registry database.

The Tenets of the Helsinki Declaration were followed. Ethical Committee approval was not required for this audit.

Results

Primary therapy

Baseline data

Forty patients (18 female; 22 male) with a mean age of 61 years (range 24–88 years) were included in this audit and are described in detail elsewhere.[2] The tumour involved the right eye in 18 patients and the left eye in 22 patients (Figure 1a). Three patients had multiple tumours and 20 had mixed tumours (ie, invasive melanoma and diffuse intra-epithelial neoplasia). The median largest basal tumour diameter was 6.8 mm and the median tumour thickness was 2.2 mm. Twenty tumours involved the cornea. The peripheral tumour margin was located in bulbar conjunctiva (31), plica (1), caruncle (5), palpebral conjunctiva (1), eyelid margin (1), and skin (1). Six tumours involved the caruncle. The TNM stage according to the 6th edition was: I (11 patients); II (20 patients); III (8 patients); and IV (1 patient).[28]

The primary treatment received by each patient is shown in Figure 1a.

Outcomes

The median time to the last known ocular status was 2.7 years. The median time to death or to the 15 June 2007 was 4.4 years.

Any ocular disease recorded after treatment is shown in Figure 1. Figure 2 shows the last known visual acuity related to the initial visual acuity and the main causes of visual loss. In most patients, the last known visual acuity was similar to that recorded before treatment. Not one of the forty patients required enucleation or exenteration.

Six patients developed invasive conjunctival tumour recurrence, with one subsequently developing lacrimal sac involvement. A cumulative 'bubble plot' and log-rank analysis correlated local tumour recurrence with medial tumour location ($P=0.004$) (Figure 3). One patient subsequently developed recurrence in the lacrimal sac. Invasive recurrence occurred in 5/21 patients treated without radiotherapy as compared to only 1 of 19 patients receiving radiotherapy. This patient (Case 3) developed recurrence outside the irradiated area. After excluding this case, log rank analysis indicated that radiotherapy lowered the risk of local tumour recurrence at the site of the primary tumour ($P=0.03$). The recurrent tumours were treated with excision and cryotherapy (one patient); external beam radiotherapy (one patient); proton beam radiotherapy (one patient) and brachytherapy (three patients). Seven patients received therapy for diffuse intra-epithelial neoplasia more than 3 months after treatment of the primary invasive tumour.

Regional lymph node metastasis was present at initial diagnosis in one patient (Patient 33) and developed

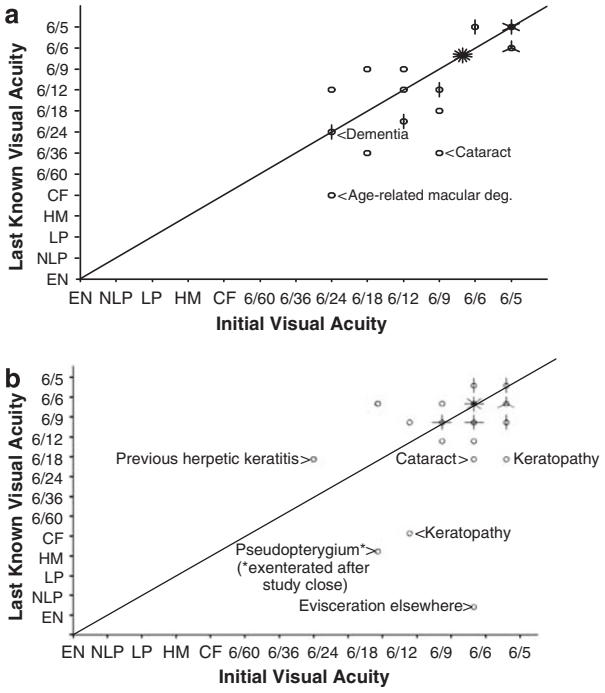

Figure 2 Last known visual acuity according to initial vision in 40 patients referred with untreated melanoma. (a) Previously untreated patients. (b) Patients referred after treatment elsewhere.

following treatment in two patients (Patients 25 and 34), after 22 and 34 months, respectively.

Four patients (Patients 3, 8, 16, and 17) died of metastatic disease. A cumulative plot indicated that compared to patients without metastatic death, these patients were more likely to have involvement of the medial conjunctiva by their tumour (Figure 3c). Log-rank analysis correlated caruncular involvement with metastatic death ($P < 0.001$) (Figure 3d). Two patients had developed recurrent local disease. Five patients with TIII disease were alive at the close of the audit, one of whom developed regional lymph node metastasis. Three of these patients did not have caruncular involvement and three had less than 5 years' follow-up. Seven patients died of unrelated causes, which were: breast carcinoma; cerebrovascular disease; cardiac failure; pulmonary embolism; diabetic complications; pneumonia; and myocardial infarction.

Salvage therapy

Baseline data

Thirty-six patients were referred for salvage therapy after undergoing tumour biopsy or excision elsewhere. These patients (17 female, 19 male) had a median age of 64.6

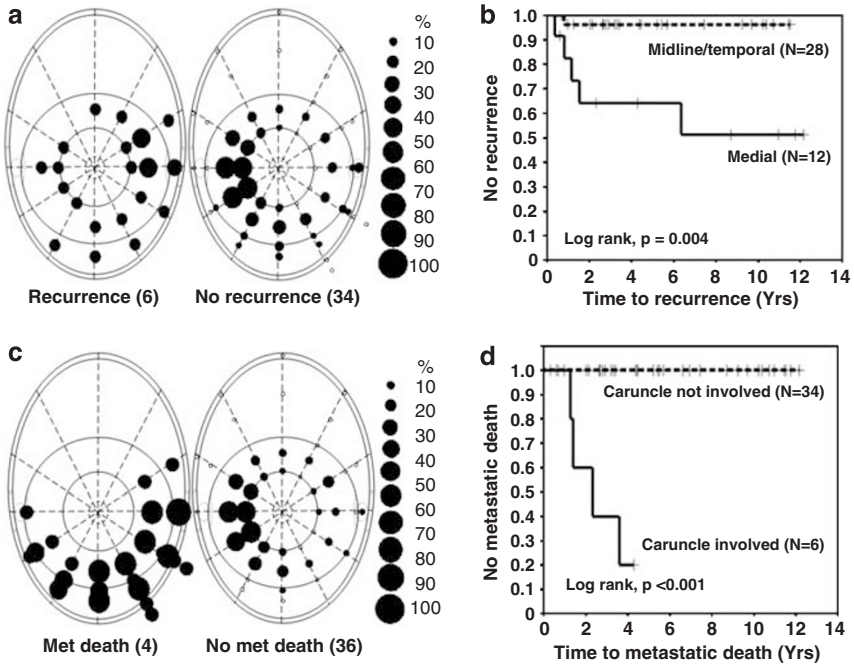

Figure 3 (a) Cumulative 'bubble plot' showing distribution of invasive conjunctival melanoma according to local tumour recurrence.[2] Each bubble indicates an area of conjunctiva, with the size of the bubble indicating the percentage of patients showing tumour involvement of that area. (b) Kaplan–Meier curves showing time to local tumour recurrence according to coronal tumour location. (c) Cumulative 'bubble plot' correlating distribution of invasive conjunctiva with metastatic death. (d) Kaplan–Meier curves showing time to metastatic death according to involvement of caruncle. In a and c, results from left eye were transposed to right eye.

years (mean 63.0, range 37–83). The visual acuity at first assessment at our centre was 6/9 or better in 31 patients, 6/12–6/18 in four patients, and 6/36 in one patient, who had a history of herpetic keratitis. At the time of referral, 11 patients had a conjunctival scar with no evident tumour; 9 showed only intra-epithelial neoplasia (the invasive tumour having been excised); 10 had invasive melanoma; and 6 had both invasive melanoma and intra-epithelial neoplasia (Figure 1b). The caruncle was involved in two patients. The invasive tumour or scar was lateral in 20 patients, medial in 15 patients, and of uncertain location in two patients (Figure 1b). The initial TNM 'T' category at the time of referral was estimated (albeit imprecisely in some patients) to be: I (18 patients); II (16 patients); III (1 patient); and IV (1 patient). Four patients (Patients 9, 10, 14, and 33) were referred with the first recurrence and three patients (Patients 1, 3, and 6) referred with a repeat recurrence. One patient (Patient 14), who was referred with a recurrent tumour, had been treated for pre-auricular nodal involvement 2 years previously.

Ocular morbidity at the time of referral to our centre included: epiphora (one patient); cataract (two patients); corneal scarring (one patient); entropion (1 patient); glabellar flap (one patient); ptosis (1 patient); herpetic keratitis (two patients); plomb for iatrogenic retinal tear during tumour excision (one patient); ophthalmic herpes zoster (one patient); symblepharon (one patient); and pterygium (one patient). One patient had no perception of light in the fellow eye, because of central retinal vein occlusion. Patient management is summarised in Figure 1b.

Outcomes

In the conjunctival melanoma patients treated with salvage therapy, the median time to the last known ocular status was 1.6 years (range 0–6.98). The median time to death or to the 15 June 2007 was 3.2 years (range 0.7–13.9).

Ocular morbidity developing after our treatment is shown in Figure 1b. The last known visual acuity was 6/12 or worse in eight patients (Figure 2b). The causes of visual loss are shown in Figure 2b. One patient with keratopathy was eviscerated elsewhere because of discomfort. After the close of this study, one patient (Patient 5) had exenteration for local tumour recurrence with an uncomfortable eye.

Six patients developed recurrent invasive disease after our salvage therapy. Four of these had initially been referred to us with recurrent disease. In these four patients, the recurrences were located in conjunctiva (Patients 5, 6, and 14) or orbit (Patient 1, treated by local excision). Six patients were subsequently treated for intra-epithelial neoplasia, which was located at the primary site in two and in other areas in four.

Patients 1 and 7 developed nodal metastasis, both 21 months after referral.

Five patients (Patients 1, 3, 6, 10, 14) died of metastatic disease (median delay 69 months, range 29–71). All had visible, recurrent, invasive melanoma at the time of referral to our centre. The TNM 'T' category of these patients was I (Cases 3 and 14), II (Cases 6 and 10), and IV (Case 1). Patient 9 died of myocardial infarction.

Discussion

Our audit showed that all forty patients receiving initial treatment at our centre retained the eye. Local tumour recurrence was rare and was associated with medial tumour location and lack of radiotherapy. Metastatic death correlated with caruncular involvement. Almost 50% of patients referred to us had previously undergone biopsy or excision elsewhere. Several of these patients were referred with recurrent invasive melanoma and these tended to have a worse outcome in terms of local tumour control and survival.

Our audit was facilitated by a system for tumour mapping. As we developed this only recently, tumour extent was mapped only retrospectively, although we feel that our records enabled reasonable accuracy. This audit was also enhanced by differentiating patients receiving primary treatment at our centre from those referred after surgery elsewhere. The main weakness of our audit was the short follow-up, although the data were sufficient to demonstrate significant correlations with local tumour control and survival.

After our primary treatment, local recurrence at the primary tumour site occurred only in patients who did not receive radiotherapy. This result supports our shift away from adjunctive cryotherapy to adjunctive radiotherapy and chemotherapy. Our rates of local tumour control seem relatively good, but comparisons with published articles were limited by inadequate tumour staging in other studies and considerable variation in follow-up.

Five of the nine patients who died of metastatic disease had caruncular involvement, which is a well-known indicator of poor prognosis. It is noteworthy that the four patients with non-caruncular, bulbar tumours who died of metastasis had all been referred to us with recurrent invasive melanoma. Previous studies report a correlation between local recurrence and metastasis.[15,25] Although the fatal tumours may have been unusually malignant from the outset, it is also possible that inadequate treatment contributed to mortality.

Only two patients who died of systemic metastases had overt regional nodal involvement, which undermines the scope of sentinel node biopsy.[22,29]

None of our patients developed intraocular spread of melanoma.[30,31] This is perhaps because of prompt administration of adjunctive brachytherapy and because we did not perform lamellar corneo-scleral excision (which also causes cosmetic deformity). Notably, only one of our patients required exenteration, which has been necessary in up to 20% of patients in other studies.[15,32] Our patient requiring exenteration was referred in 1995 after treatment elsewhere and we had treated her with adjunctive cryotherapy, which we have since abandoned.

We were able to treat all patients satisfactorily without amniotic membrane grafts.[33,34] This is because we created conjunctival rotation flaps and allowed some eyes to heal by second intention (ie, leaving an area of bare sclera to heal spontaneously).

Our suspicion is that patients who initially underwent a surgical intervention before referral to our centre did relatively poorly because of iatrogenic tumour seeding. We caution against incisional biopsy of possible conjunctival melanomas and encourage no-touch, *en-bloc* tumour excision, preserving natural barriers such as Bowman's membrane, using fresh instruments for conjunctival closure, adjunctive brachytherapy for deep invasion, and topical chemotherapy for intra-epithelial neoplasia. Because of the high rates of local recurrence reported in the literature, we currently administer adjunctive brachytherapy irrespective of whether or not the tumour appears histologically to be completely excised. Others have expressed concerns about inexpert treatment of conjunctival melanoma.[15,35] Patients with a suspected conjunctival melanoma should ideally be referred to an ocular oncology centre for treatment, preferably without incisional biopsy or any attempts at tumour excision at the home hospital.

We did not attempt to classify invasive melanomas according to whether they arose from a pre-existing naevus or *de novo*. This is because it is often difficult or impossible to determine whether or not a pre-existing naevus was present. We prefer to categorise invasive melanomas according to prognostic factors such as: (1) whether the tumour is circumscribed or diffuse and (2) whether or not there is associated intra-epithelial neoplasia (ie, primary or secondary to the invasive disease).

We found clinically overt, diffuse, intra-epithelial melanocytic neoplasia in about 50% of all previously untreated, invasive conjunctival melanomas. Such intra-epithelial disease comprised primary *in situ* melanoma and/or secondary pagetoid spread from the invasive tumour. The existence of *in situ* conjunctival melanoma is not widely acknowledged in ophthalmology, but must exist, because invasive conjunctival melanoma arises from epithelium, so that there has to be an *in situ* phase even if this is not always recognised clinically. Our view is supported by the fact that conjunctival intra-epithelial melanocytic neoplasia is histologically similar to cutaneous and mucosal *in situ* melanomas.
Some authors have expressed concerns that the term '*in situ* conjunctival melanoma' might alarm ophthalmologists and patients;[36] however, the term 'primary acquired melanosis (PAM) with atypia' may give false reassurance to ophthalmologists and patients and may mislead non-ophthalmologists involved in the patient's care (eg, family doctor, plastic surgeon). As a result, *in situ* melanoma may inadvertently be under-treated just when opportunities for eradicating malignancy are greatest.

Our results highlight several shortcomings in the current 6th edition of TNM staging for conjunctival melanomas (Table 1). We have therefore devised a new system to overcome these limitations. First, our proposed staging system takes account of tumour size, using circumferential spread, because it is easier to measure angle in minutes than distance in millimetres. Second, as none of 20 patients with corneal involvement developed metastases, in keeping with other studies, we have excluded this as a risk factor.[37] Third, our system takes account of the finding that caruncular involvement significantly worsens the survival prognosis. Fourth, our proposed system does not group all non-conjunctival disease equally; for example, we stage tumours with intracranial spread as having a worse prognosis than those with only eyelid skin involvement. Fifth, we do not assume that intraocular spread has a poor prognosis for survival, because the eye is devoid of lymphatics. Finally, our system includes 'conjunctival *in situ* melanoma' (ie, Tis stage), which we consider an essential precursor of invasive disease.

There is scope for further studies. First, it would be useful to document *in situ* melanoma more objectively, avoiding vague terms such as 'mild', 'moderate', and 'severe'. We have developed a scoring system based on intra-epithelial spread, melanocytic density, and cellular atypia and are currently evaluating this method (Damato and Coupland, Clinical Experimental Ophthalmology, submitted). Second, there is a need for long-term studies correlating baseline disease with local tumour control and survival, so that staging systems can be based on evidence instead of intuition. Thirdly, we need to understand why medial tumours and particularly those involving caruncle have worse prognosis, so that metastatic disease might be prevented more effectively.

In conclusion, primary treatment of conjunctival melanoma at a specialised ocular oncology centre achieves high rates of local tumour control with conservation of the eye and vision. Adjunctive brachytherapy and topical chemotherapy are valuable. Future TNM staging of conjunctival melanoma should take account of caruncular involvement, which correlates with high mortality. Inadequate surgical interventions may cause local tumour recurrence and metastatic death.

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