Conjunctival Melanoma

Risk Factors for Recurrence, Exenteration, Metastasis, and Death in 150 Consecutive Patients

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Objective: To identify the risk factors of conjunctival malignant melanoma that predict local tumor recurrence, orbital exenteration, distant metastasis, and tumor-related mortality.

Design: The clinical parameters of the patient, tumor, and treatment were analyzed in a nonrandomized fashion for their relation to 4 main outcome measures using Cox proportional hazards regression models.

Participants: One hundred fifty consecutive patients.

Main Outcome Measures: Local tumor recurrence, orbital exenteration, distant metastasis, and death from conjunctival melanoma.

Results: The Kaplan-Meier estimates of local tumor recurrence was 26% at 5 years, 51% at 10 years, and 65% at 15 years. The mean number of recurrences per patient was 1 (median, 0 recurrences). There was no recurrence in 98 patients (65%), 1 recurrence in 28 patients (19%), 2 recurrences in 11 patients (7%), 3 recurrences in 5 patients (3%), and 4 or more recurrences in 8 patients (5%). Using multivariate analysis, the factors correlated with local tumor recurrence were melanoma location (not touching the limbus) (P = .01) and pathological tumor margins (lateral margin involved) (P = .02). Multivariate analysis for features correlated with ultimate exenteration included initial visual acuity (20/40 OU or worse) (P < .001), melanoma color red (P = .01), and melanoma location (not touching the limbus) (P = .02).

Tumor metastasis was present in 16% of patients at 5 years, 26% of patients at 10 years, and 32% of patients at 15 years. Metastasis was first located in the regional lymph nodes in 17 cases, the brain in 4 cases, the liver in 3 cases, the lung in 2 cases, and was disseminated in 1 case. The risks for metastases using multivariate analysis included pathological tumor margins (lateral margin involved) (P = .002) and melanoma location (not touching limbus) (P = .04).

Tumor-related death occurred in 7% patients at 5 years' follow-up and 13% at 8 years' follow-up. The risk factors for death using multivariate analysis included initial symptoms (lump) (P = .004) and pathologic findings (de novo melanoma without primary acquired melanosis) (P = .05). The technique of initial surgery was shown to be an important factor in preventing eventual tumor recurrence (P = .07), metastasis (P = .03), and death (P = .006) in the univariate analysis, but did not reach significance in the multivariate analysis.

Conclusions: Conjunctival malignant melanoma is a potentially deadly tumor. In the present study, metastasis was detected in 26% of patients, and death occurred in 13% of patients at 10 years. Extralimbal melanoma and tumor involvement of the surgical margins were especially poor prognostic factors. Meticulous surgical planning using wide microsurgical excisional biopsy working with the “no touch” technique and supplemental alcohol corneal epitheliectomy and conjunctival cryotherapy is advised.

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PATIENTS AND METHODS

The computerized diagnostic coding records of all patients evaluated at the Oncology Service, Wills Eye Hospital, Philadelphia, Pa, from April 1974 to September 1997 were reviewed. All patients with the diagnosis of conjunctival melanoma were identified and included in this analysis. Each case was analyzed according to specific clinical and pathological features. The variables marked with a (†) were used as reference in the univariable and multivariable analysis.

The clinical variables included patient age, race (Caucasian†, African American), sex (male†, female), eye (right†, left), signs and symptoms (spot†, lump, irritation, other, none), medical history (cutaneous melanoma, dysplastic nevus syndrome, uveal melanoma, neurofibromatosis, acquired immunodeficiency syndrome, and others), family history (conjunctival melanoma, cutaneous melanoma, dysplastic nevus syndrome, uveal melanoma, neurofibromatosis, and others), cutaneous complexion (fair white†, olive white, nonwhite), and prior systemic treatment (chemotherapy, corticosteroids, ocular radiation). Prior management of the tumor before referral was assessed for type of surgical technique (incisional biopsy, excisional biopsy†, cryotherapy, alcohol corneal epithelectomy) and number of prior recurrences. The general ocular clinical features included visual acuity, iris color (blue†, green, brown), eyelid lentigo maligna (present, absent†), and associated PAM and its extent (number of clock hours involved). The tumor features at initial patient visit included melanoma quadrant location (superior, nasal, inferior, lateral†, diffuse), melanoma anatomic conjunctival location (bulbar†, fornix, tarsus, plica semilunaris, caruncle), melanoma bulbar extension (number of clock hours involved), melanoma proximity to limbus (in millimeters), radial corneal involvement by melanoma (in millimeters), and depth of corneal involvement by melanoma (epithelium†, stroma, Descemet membrane). Additional clinical tumor features included melanoma base size (in millimeters), melanoma thickness (in millimeters), melanoma color (brown†, red, yellow, variable), melanoma feeder vessels (present, absent†), initial tumor surgery after referral (incisional biopsy, excisional biopsy†, cryotherapy, alcohol corneal epithelectomy, exenteration), local melanoma recurrence (number), orbital melanoma recurrence (number), eventual orbital exenteration (yes, no†), and final visual acuity. Melanoma recurrence was defined as the development of a new histopathologically confirmed malignant melanoma at any site on the conjunctiva or ocular adnexa after prior surgical treatment. The site of recurrence could be the same or different than prior tumors. Histopathologically proven melanoma metastasis and melanoma-related death was recorded.

The histopathological data were recorded from pathology reports submitted to the clinician on the clinical record. The features analyzed included melanoma thickness by gross examination (in millimeters), melanoma surgical margins by microscopic examination (base involved, lateral margin involved, margins clear†), and microscopic features associated with melanoma (nevus, PAM, none†).

The clinical and histopathological parameters were analyzed as they affected 4 end points, including local melanoma recurrence, orbital exenteration, melanoma metastases, and melanoma-related death. Melanoma recurrence was defined as the development of a new tumor that was histopathologically confirmed to be a malignant melanoma, at any location on the surface of the eye or in the orbit. Recurrence, therefore, implied reappearance of the disease at any site, rather than reappearsence of a specifically treated tumor. The variables were analyzed with regard to the first and second recurrence of the disease.

A series of univariate Cox proportional regression analyses were performed to assess the individual parameters as they affected each of the 4 major end points. All variables were analyzed as discrete variables except for age at initial visit, number of recurrences before referral, initial visual acuity, proximity of melanoma to the corneo-scleral limbus, melanoma radial corneal involvement, melanoma base and thickness, total number of local melanoma recurrences, and histopathologic gross tumor thickness, which were analyzed as continuous variables and later grouped into discrete categories to derive cut-off values. In addition, clock-hour extension of PAM and melanoma were analyzed as ordinal variables and later grouped into discrete categories. A preliminary stepwise model included all of the variables that were significant on a univariate level (P ≤ .10) to determine an independent set of predictors for each outcome in the final multivariate model. Kaplan-Meier survival estimates of the probability of developing recurrence, orbital exenteration, metastasis, and death as a function of time from initial examination at the Oncology Service were performed.31

Without access to the full context or additional details, it is challenging to provide a comprehensive summary. However, the text appears to discuss the analysis of clinical and histopathological features related to the management and outcomes of conjunctival melanoma. It highlights the evaluation of various factors such as patient demographics, clinical symptoms, and tumor characteristics, with an emphasis on recurrence and treatment outcomes. The discussion includes statistical methods for analyzing the data and determining predictors of patient mortality or patient outcome. The text also touches on the surgical aspects and management strategies for this rare condition, noting the necessity for further research and clinical guidelines.

noma and analyzed the effects of these features on patient outcome. It has been recognized that the pathological factors predictive of patient mortality from conjunctival melanoma include increasing tumor thickness, involvement of the palpebral, caruncular, or fornical conjunctiva, mixed cell type, lymphatic invasion, and increasing mitotic activity. In addition, those tumors with associated primary acquired melanosis (PAM) that demonstrated a pagetoid growth pattern, atypical melanocytes, full-thickness epithelial involvement, and absence of inflammatory response carried a worse prognosis.581314 Most prior reports on conjunctival melanoma have had limited information on clinical details of the patient or the tumor, often because the clinical features were extracted from pathology forms or cancer registry questionnaires. General details such as patient age, race, and sex, as well as tumor location, have been investigated, but specific details of the tumor itself or its effect on surrounding tissues, extent of associated PAM, and many other important clinical features have not been addressed. In addition to the lack of clinical details, there is a lack of information regarding the surgical approach to these malignancies. In most prior reports, there have generally been many clinicians using various surgical techniques for tumor management with little if any of this vital information included in the analysis of tumor control or patient outcome.

Few clinicians have the opportunity to manage more than 1 case of conjunctival malignant melanoma during their years of clinical practice. The techniques for surgical management of this rare tumor have slowly evolved over time, mainly in major ocular oncology centers. Some
portions of the treatment of conjunctival melanoma is based on concepts learned from dermatologic management of the more common cutaneous malignant melanoma. However, most of the techniques that we presently use are based on nearly 25 years of experience treating conjunctival and other ocular tumors.

In this report, we analyze our personal clinical experience with 254 conjunctival malignant melanomas in 150 consecutive patients. We investigate, in detail, the features of the patient and tumor and our surgical approach for tumor management in an effort to better understand the clinical factors of conjunctival melanoma as they affect tumor recurrence and metastasis.

RESULTS

Throughout a period of 23 years, from April 1974 to September 1997, we have managed 254 conjunctival malignant melanomas in 150 patients at the Oncology Service at Wills Eye Hospital. The mean length of follow-up provided by the Oncology Service alone was 4.2 years (range, 1 month-20.2 years). The mean overall patient length of follow-up provided by the Oncology Service along with the referring physician was 7.0 years (range, 1 month-35.3 years).

The mean age at first visit was 60 years (median, 62 years; range, 16-89 years). Of all patients, 2 (1%) were younger than 20 years, 18 (12%) were aged 21 to 40 years, 49 (33%) were aged 41 to 60 years, and 80 (54%) were older than 60 years at initial visit. All patients were Caucasian except for 1 African American. In the Caucasian patients, the skin complexion was judged to be light (fair) in 148 (99%) and dark (olive) in 1 patient (1%). There were 75 male patients (50%) and 75 female patients (50%). In all cases, the disease was unilateral. The right eye was involved in 67 patients (45%) and the left eye in 83 patients (55%).

The main signs and symptoms as noted by the patient included a spot in 116 patients (77%), a lump in 91 eyes (61%) and did not reach the limbus in 56 eyes (37%). Of those tumors classified as bulbar melanoma, the mean proximity of the melanoma to the limbus was 2 mm (median, 2 mm; range, 0-8 mm). The iris color was blue in 47 eyes (31%), green in 17 eyes (11%), brown in 85 eyes (57%), and not specified in 1 eye (1%). Ipsilateral conjunctival PAM was present with the conjunctival melanoma in 67 patients (45%), and the extent of involvement was less than 3 clock hours in 19 patients (13%), 4 to 6 clock hours in 27 patients (18%), 7 to 9 clock hours in 10 patients (7%), and 10 to 12 clock hours in 11 patients (7%).

The melanoma location was classified as superior in 24 cases (16%), medial in 26 cases (17%), inferior in 33 cases (22%), lateral in 63 cases (63%), and diffuse in 4 cases (3%). The location of the tumor epicenter was bulbar in 138 cases (92%), fornix in 4 cases (3%), palpebral in 6 cases (4%), plica semilunaris in 1 case (1%), and caruncle in 1 case (1%). The melanoma extent was 1 clock hour or less in 18 patients (12%), 2 clock hours in 61 patients (41%), 3 clock hours in 37 patients (25%), 4 clock hours in 13 patients (9%), 5 clock hours in 7 patients (5%), and 6 or more clock hours in 7 patients (5%). Of those tumors classified as bulbar melanoma, the mean proximity of the melanoma to the limbus was 2 mm (median, 2 mm; range, 0-8 mm). The tumor touched the limbus in 91 eyes (61%) and did not reach the limbus in 56 eyes (37%). Information regarding exact proximity to the limbus was not available in 3 cases (2%). Of those tumors with corneal involvement, the mean amount of radial involvement onto the peripheral cornea was 1 mm (median, 1 mm; range, <1-9 mm). When the cornea was involved with melanoma, the depth of invasion was into the corneal epithelium in all cases except 1, in which stromal involvement was detected. In no cases was intraocular invasion detected at initial visit.

The mean tumor base from a clinical standpoint was 8 mm (median, 8 mm; range, 2-20 mm) and the mean tumor thickness was 2 mm (median, 2 mm; range, 1-15 mm). The melanoma was classified as brown in 102 cases (68%), red in 16 cases (11%), yellow in 29 cases (19%), and a combination of brown and yellow in 3 cases (2%) (Figure 1). Tumor feeder vessels were present in 38 cases (39%) and absent in 91 cases (61%).

The initial surgical approach to the tumor after referral to our service was incisional biopsy in 0 cases (0%), excisional biopsy alone in 27 cases (18%), excisional biopsy and cryotherapy in 46 cases (31%), excisional biopsy, cryotherapy, and alcohol corneal epithelectomy in 65 cases (43%), orbital exenteration in 7 cases (5%), and observation in 5 cases (3%) (Figure 2 and Figure 3). Eventual orbital exenteration was performed in a total of 20 patients (13%). The final visual acuity in the involved eye after all treatments at last follow-up was 20/20 in 52 patients (35%), 20/25 in 26 patients (17%), 20/30 in 13 patients (9%), 20/40 in 6 patients (4%), 20/50 in 6 patients (4%), 20/70 in 1 patient (1%), 20/80 in 1 pa-
tient (1%), 20/100 in 3 patients (2%), 20/200 in 5 patients (3%), and 20/400 or worse (including 20 exenteration patients) in 30 patients (20%).

Histopathologically, the mean tumor thickness by gross examination was 2 mm (median, 2 mm; range, 1-12 mm). By report, the surgical margins were judged clear of tumor in 89 cases (59%), lateral margin involved with tumor in 11 cases (7%), base involved in 13 cases (9%), both lateral and base involved in 4 cases (3%), and margins not specified in 33 cases (22%) (Figure 4). In addition to the conjunctival melanoma, there was an associated conjunctival nevus in 6 cases (4%), PAM in 80 cases (53%), no associated lesions in 55 cases (37%), and not specified in 9 cases (6%).

Figure 1. Clinical appearance of conjunctival melanoma. A, Pigmented conjunctival melanoma at the corneoscleral limbus. B, Nonpigmented recurrent conjunctival melanoma at the corneoscleral limbus.

Figure 2. Surgical treatment of conjunctival melanoma. A, Before surgery, note that the tumor extends from the 12:30 to the 5:00 position at the limbus and involves the corneal epithelium. B, After surgery (alcohol corneal epitheliotomy and excisional biopsy using “no touch” technique and supplemental cryotherapy), the conjunctival surface has healed well with no tumor recurrence over the 10-year follow-up. Note the mild dragging of conjunctival tissue at the resection site.

Figure 3. Recurrent conjunctival melanoma. A, Multiple pigmented recurrent tumors are noted along the bulbar conjunctival fold in a patient who had previous biopsy at another hospital several months earlier. B, Amelanotic extralimbal recurrence in a patient who had several previous excisional biopsies of conjunctival melanoma.
With regard to the 4 end points of tumor recurrence, orbital exenteration, tumor metastasis, and patient death, the results will be discussed separately in the following sections.

RECURRENT

Of the 150 patients, 98 (65%) had no tumor recurrence, and 52 patients (35%) experienced recurrence. The total number of local melanoma recurrences was 1 in 28 patients (19%), 2 in 11 patients (7%), 3 in 5 patients (3%), 4 in 3 patients (2%), and 5 or more in 5 patients (3%). The mean number of recurrences per patient was 0 (median, 1 recurrence; range, 0-8 recurrences).

Using Kaplan-Meier survival estimates, recurrence was detected in 26% at 5 years’ follow-up, 51% at 10 years’ follow-up, and 65% at 15 years’ follow-up (Figure 5). The mean interval from first to second recurrence was 15 months (median, 9 months; range, 1-49 months). The mean interval from second recurrence to third recurrence was 15 months (median, 15 months; range, 1-41 months).

In a series of univariate analyses, the factors correlated with recurrence of conjunctival melanoma included melanoma not touching the limbus (P = .001), melanoma more than 2 mm from the limbus (P = .001), extent of PAM for 7 to 9 clock hours (P = .004), melanoma located in the superior quadrant (P = .02), lateral and base margins of pathologic specimen involved with tumor (P = .03), clinical tumor thickness greater than or equal to 2 mm (P = .03), and corneal involvement with melanoma greater than or equal to 2 mm (P = .04). Using univariate analysis, the risk for second recurrence of melanoma included melanoma not touching limbus (P = .004), PAM involving 7 to 9 clock hours (P = .005) and 4 to 6 clock hours (P = .03), melanoma involving the cornea (P = .009), surgical technique using incisional biopsy prior to referral (P = .04), and melanoma quadrant superior (P = .02).

A multivariate analysis showed that the factors related to tumor recurrence included melanoma location not touching the limbus (P = .01) and pathologic evidence of tumor to the lateral margin (P = .02) (Table 1).

ORBITAL EXENTERATION

Of the 150 patients, 20 (13%) were eventually treated with orbital exenteration during this study. Of the 20 exenterations, 7 were performed at the initial surgery, 6 after the first recurrence was detected, 3 after the second recurrence, 2 after the third recurrence, and 2 after 4 or more recurrences. Using Kaplan-Meier survival es-

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Table 1. Multivariate Analysis of Clinical Factors Correlated With First Local Tumor Recurrence in 150 Patients With Conjunctival Malignant Melanoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>P</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma touching limbus (yes* vs no)</td>
<td>.01</td>
<td>2.3 (1.2-4.6)</td>
</tr>
<tr>
<td>Pathology tumor margins</td>
<td>.02</td>
<td>2.9 (1.2-7.1)</td>
</tr>
<tr>
<td>(lateral margin involved vs base involved, lateral and base involved, and margins clear*)</td>
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*Asterisk indicates the reference variable.
mates, exenteration was performed in 8% of patients by 5 years’ follow-up, 16% by 10 years’ follow-up, and 32% by 15 years’ follow-up (Figure 6). Using univariate analyses, the risks for eventual orbital exenteration included visual acuity of 20/40 to 20/100 (P=.001), corneal involvement with melanoma greater than or equal to 2 mm (P=.002), melanoma quadrant inferior (P=.003) or superior (P=.04), clinical tumor thickness greater than or equal to 2 mm (P=.004), melanoma not touching limbus (P=.005), prior surgery before referral of excisional biopsy alone without adjuvant cryotherapy (P=.006), pathologic features showing de novo origin of the tumor (P=.02), melanoma location in the fornix (P=.02), and sign and symptoms of a lump (P=.03).

Using multivariate analysis, the risks for eventual orbital exenteration included initial visual acuity of 20/40 to 20/100 (P=.001), 20/200, or worse (P=.01) compared with visual acuity of 20/20 to 20/40, melanoma color red (P=.01), and melanoma not touching the limbus (P=.02) (Table 2).

**Table 2. Multivariate Analysis of Clinical Factors Correlated With Eventual Orbital Exenteration in 150 Patients With Conjunctival Malignant Melanoma**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk (95% Confidence Interval)</th>
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<tbody>
<tr>
<td>Initial visual acuity</td>
<td>&lt;.001 (8.1 (2.4-27.5))</td>
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<tr>
<td>(20/20-20/30* vs 20/40-20/100)</td>
<td></td>
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<tr>
<td>Initial visual acuity</td>
<td>.01 (5.8 (1.4-22.2))</td>
</tr>
<tr>
<td>(20/20-20/30* vs 20/200 or worse)</td>
<td></td>
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<tr>
<td>Melanoma color</td>
<td>.01 (6.0 (1.5-24.0))</td>
</tr>
<tr>
<td>(brown* vs red)</td>
<td></td>
</tr>
<tr>
<td>Melanoma touching limbus</td>
<td>.02 (3.3 (1.1-9.9))</td>
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<tr>
<td>(yes* vs no)</td>
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* Asterisk indicates the reference variable.

Of the 150 patients, 27 (18%) eventually developed metastasis. Using Kaplan-Meier survival estimates, metastasis was detected in 16% of patients by 5 years’ follow-up, 26% by 10 years’ follow-up, and 32% by 15 years’ follow-up (Figure 7). The location of the first detectable metastatic focus was facial lymph nodes in 17 patients, the lung in 2 patients, the brain in 4 patients, the liver in 3 patients, and was disseminated in 1 patient. Of those with facial lymph node involvement, the cervical nodes were first involved in 10 patients, preauricular nodes in 5 patients, submandibular nodes in 1 patient, and unspecified nodes in 1 patient.

Using univariate analyses, the variables correlated with tumor metastasis included melanoma quadrant inferior (P<.001) and superior (P=.02), pathologic evidence of tumor involving the lateral margin (P=.002) and lateral and base margins (P=.02), melanoma not touching the limbus (P=.01), melanoma greater than or equal to 2 mm from the limbus (P=.03), initial surgical technique of excisional biopsy without cryotherapy and alcohol corneal epitheliectomy (P=.03), and right eye (P=.04). Using multivariate analysis, the risk factors for metastasis included pathologic evidence of lateral tumor margin involved (P=.002) and melanoma not touching the limbus (P=.04) (Table 3).

**Table 3. Multivariate Analysis of Clinical Factors Correlated With Tumor Metastasis in 150 Patients With Conjunctival Malignant Melanoma**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
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<tbody>
<tr>
<td>Pathology tumor margins</td>
<td>.005 (5.7 (1.7-19.0))</td>
</tr>
<tr>
<td>(base involved, lateral and base involved, and clear* vs lateral margin involved)</td>
<td></td>
</tr>
<tr>
<td>Melanoma touching limbus</td>
<td>.03 (3.1 (1.1-8.5))</td>
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<tr>
<td>(yes* vs no)</td>
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* Asterisk indicates the reference variable.

**DEATH**

Of the 150 patients, 12 (8%) died of metastatic melanoma. Using Kaplan-Meier survival estimates, death oc-
Toxicity to the eye; 7% of the patients experienced aggressive features of melanoma.

In 1977, Zimmerman22 delivered the first Algernon B. Reese Lecture entitled “The Histogenesis of Conjunctival Melanomas.” In this essay, he provided criteria for the application of histopathologic findings to clinical features of conjunctival melanoma. These criteria have provided a better understanding and improved recognition of conjunctival melanoma and its precursors. Later, Crawford23 studied prognostic features related to metastasis of conjunctival melanoma in 19 patients. He reported these results at the American Ophthalmologic Society and identified young age, tumor location in the caruncle, fornix, or palpebral conjunctiva, high mitotic activity, and lack of inflammation on pathology to be related to worse prognosis. Jakobiec24 later presented at the American Ophthalmologic Society an extensive study on the details of the ultrastructure of conjunctival malignant melanoma and its precursors. These reports and others have added substantially to our understanding of the microscopic features and behavior of conjunctival melanoma.

The classic description of conjunctival melanoma is that of a brown to tan elevated mass on the bulbar conjunctiva surrounded by a bed of flat, PAM in a middle-aged patient.16,17,24,25 In this study of 150 cases, the mean tumor size was 8 mm at the base and 2 mm in thickness, and the most characteristic location for the tumor was on the bulbar conjunctiva (92%) in the temporal quadrant (63%). The tumor usually touched the limbus (61%) and generally involved about 2 clock hours of conjunctiva (41%). The tumor was typically brown (68%) and often had prominent feeder vessels (39%). These features were strongly suggestive of the diagnosis. However, less typical appearances of conjunctival melanoma should be recognized, and these include presentation as a mass in the tarsus (4%), fornix (3%), plica semilunaris (1%), or caruncle (1%).26 Lack of pigmentation in the mass, imparting a yellow or reddish pink appearance to the tumor was found in 30% of cases, more often in those patients with prior excisions. Recurrent conjunctival melanoma often presents as an amelanotic mass and may be mistaken for a pyogenic granuloma in a patient with multiple prior conjunctival melanoma excisions.

Conjunctival melanoma is proposed to originate from preexisting conjunctival nevus, PAM, or de novo melanoma.7,27-29 Our results disclosed histopathological evidence of possible origin from nevus in only 4% of cases, PAM in 57% of cases, and de novo in 39% of cases. Nooregaard et al11 found a slightly different distribution of nevus in 16% of cases, PAM in 36% of cases, and de novo melanoma in 47% of cases. In some instances, PAM is subtle or not pigmented therefore it may not be clinically visible and its frequency may be underestimated. Underestimation of the frequency of associated PAM can also be a problem on histopathology as the tumor can overgrow the melanosis or the melanosis may be remote to the area of tumor resection. It was somewhat surprising to find in our study that those patients with tumors arising from PAM did not show a greater risk for recurrence. One might expect more recurrences, a more complex course, and a greater risk for exenteration in melanomas arising from PAM, but in fact, those tumors that arose de novo carried a greater risk for exenteration and death. It is recognized in the dermatologic literature that cutaneous melanoma that arises from lentigo maligna carries a better overall prognosis with 10% regional metastases as compared with approximately 30% to 50% metastatic rate with nodular cutaneous melanoma.30 Lentigo maligna is comparable with PAM, and the behavior of the malignant melanoma that they spawn may be similar.31

Table 4. Multivariate Analysis of Clinical Factors Correlated With Death in 150 Patients With Conjunctival Malignant Melanoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>P</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs/symptoms (spot* vs lump)</td>
<td>.004</td>
<td>6.2 (1.8-21.7)</td>
</tr>
<tr>
<td>Pathology associated features</td>
<td>.05</td>
<td>0.2 (0.04-1.0)</td>
</tr>
<tr>
<td>with melanoma (primary acquired melanosis vs none*)</td>
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*Asterisk indicates the reference variable.
The association of other cutaneous diseases with conjunctival melanoma and nevi has been investigated. Several authors have speculated on the relationship of simultaneous or sequential conjunctival melanoma with cutaneous melanoma and cutaneous dysplastic nevus syndrome. Bataille et al found convincing evidence of a relationship between cutaneous and ocular melanoma as well as dysplastic nevus syndrome and ocular melanoma. However, they admit that 3 of the 5 patients with cutaneous melanoma were discovered only as a result of their study and only 1 patient in their cohort had conjunctival melanoma. The remaining patients had choroidal melanoma or PAM. Dysplastic nevus syndrome and small cutaneous melanoma can be overlooked and should be investigated in all patients with uveal or conjunctival melanoma. In our study, cutaneous melanoma was present in 7 patients, and a family history of cutaneous or uveal melanoma. In our study, cutaneous melanoma was present in 7 patients and in 3 patients. The occurrence of such relatively rare tumors in the same individual would be unlikely. Others have also recognized an association among conjunctival melanoma, cutaneous melanoma, and dysplastic nevus syndrome, and have speculated that these diseases are related by embryologic, clinical, and epidemiologic factors.

It has been recently recognized that conjunctival epithelial malignant neoplasms such as squamous papilloma and squamous cell carcinoma, occur with a higher frequency in immunosuppressed patients. There were no patients in this study with conjunctival melanoma who were immunosuppressed except for 1 patient who was receiving oral corticosteroids. In addition, there were no patients with prior ocular radiotherapy.

There are few studies investigating details of the clinical features and management of conjunctival melanomas, as few clinicians have had experience with more than 1 case of this rare tumor. Lommatsch et al and coworkers reviewed the therapeutic outcome of 81 patients with conjunctival melanoma. Despite extensive, planned treatment with excision, cryotherapy and radiotherapy, they found local recurrence in 24% of cases and death from metastases at 10 years follow-up in 23% of cases, primarily related to larger tumor size. They did not analyze the effect of treatment technique or adjunctive methods such as cryotherapy or radiotherapy on patient outcome. Paridaens et al in a large review of 256 cases identified unfavorable locations for conjunctival melanoma that included palpebral, fornical, plica, caruncule, and lid margin portions of the conjunctiva. They did not assess treatment technique in their report, though they subsequently provided an exhaustive review of 95 patients in whom early orbital exenteration was found not beneficial for long-term patient outcome. They suggested that local tumor eradication, avoiding exenteration if possible, was sufficient and should be performed at an early stage. Our study demonstrated that exenteration did not affect tumor-related death.

Norregaard et al studied 55 cases of conjunctival melanoma in Denmark and found that mutilating treatment (exenteration orenucleation) showed no statistical difference in patient prognosis as compared with conservative treatment (excision with or without radiotherapy). They suggested that conservative treatment was thus reasonable when planning treatment strategy. In a prior report from our department, we found that cryotherapy as a supplement to excisional biopsy was effective in preventing tumor recurrence. The goal of the present study was to more clearly define the clinical and therapeutic risks related to unfavorable outcomes with conjunctival malignant melanoma.

In our study, local tumor recurrence was found in 26% of patients at 5 years and in 51% of patients at 10 years, similar to prior reports. Recurrence was related to tumors not touching the limbus (extralimbal) and to tumor extension reaching the margins on histopathology. In general, those tumors that touch the limbus are recognized early by the patient or physician, whereas those not touching the limbus remain hidden behind the eyelid or in the fornix, often camouflaged until the mass is large. Tumor extension and tumor margins become difficult to judge the further the mass is from the limbus and into the fornix. The surgical technique of complete excision with a wide tumor-free margin of 4 mm surrounding the melanoma is important, as residual tumor at the surgical margin could lead to recurrence. A pathology report stating the presence of melanoma to the margin of resection generally mandates reexcision of the wound using the “no touch” technique of microsurgical dissection, cryotherapy, and alcohol corneal epitheliectomy in an effort to eradicate all residual tumor cells.

In some instances, plaque radiotherapy or even topical mitomycin C is used.

In our study, the risks for orbital exenteration included poor initial visual acuity, melanoma color red, and extralimbal location of the melanoma. The first factor of poor vision probably indicates advanced or recurrent disease with multiple prior procedures performed before referral. With repeated surgery to the conjunctiva, the tissue becomes scarred, the cornea dry or astigmatic, and judgement of tumor recurrence becomes difficult. In our experience, melanoma recurrence is almost always clinically amelanotic, simulating a pyogenic granuloma, even though the original tumor may have been pigmented. Because of the lack of pigment, these tumors can remain unrecognized and progressively enlarge, especially in a patient with prior surgery and conjunctival scarring. In addition, the tumor margins of recurrent amelanotic conjunctival melanoma may be indistinct and all these factors can lead to the need for exenteration. When possible, a lid-splitting exenteration to spare the eyelids and provide rapid healing of the socket is preferred. Extensive experience with exenteration for conjunctival melanoma has found no benefit to early rather than late exenteration for patient survival. It should be realized that the indications for exenteration vary among clinicians, but in general, exenteration is advised if there is orbital invasion of tumor or extensive conjunctival tumor recurrence.

Overall, metastatic disease from conjunctival melanoma has been found in 14% to 27% of patients, and at 10 years after diagnosis, approximately 30% of patients are dead of metastases. Most of the studies investigating the clinical and pathologic factors related to metastasis and death as a result of conjunctival melanoma have come from pathology laboratories or na-
The rate of metastases in our study was 16% at 5 years' follow-up and 26% at 10 years' follow-up. The parameters correlated with metastases in our study were pathologic evidence of tumor to the surgical margins and extralimbal location of the melanoma. Throughout this study, the finding of tumor extension to the surgical margins imposed risks on the patient for local tumor recurrence, metastasis, and death. Proper surgical planning with wide tumor-free margins is important. Most (63%) of the metastases were initially detected in the facial lymph nodes. Sentinel node biopsy may be useful, but it has not yet been investigated for this disease.

Melanoma-related death occurred in 7% of patients at 5 years' follow-up and in 13% of patients at 8 years' follow-up. These results are slightly more favorable than other reports, in which a 30% to 40% death rate occurred at 10 years' follow-up. This may reflect a bias in patient selection in that the pathologically based studies may find more advanced cases than this clinically based report. This may also reflect our aggressive management of metastatic melanoma with complete lymph node dissection, as most of the metastases involved the facial lymph nodes, and often, adjuvant chemotherapy, radiotherapy, or immunotherapy were employed. With longer length of follow-up, increased mortality may be found. However, these favorable results could also indicate that treatment by experienced ocular oncologists and medical oncologists familiar with the disease, may benefit the patient's survival. In previous reports, there may have been many different surgeons providing convenient care for patients outside of major ocular oncology centers, but submitting their specimens to the pathology laboratory, thus being included in a large series. The varied experiences of the many surgeons could affect the overall patient outcome. It is important to realize that conjunctival melanoma is a very rare cancer, and few clinicians have had the clinical or surgical experience to manage more than 1 patient.

The risks for death from a univariate analysis includes type of surgery before referral, initial signs and symptoms of a lump, greater distance of the tumor from the limbus, type of surgery performed after referral to an ocular oncology center, number of local tumor recurrences, and pathological features of greater tumor thickness, microscopic margins involved with tumor, and lack of PAM with the melanoma. Even though surgical details that were significant in the univariate analysis did not appear significant in the multivariate analysis, we believe that the technique of surgery is important. The preferred surgical approach to conjunctival malignancies includes the no-touch technique of microsurgical excisional biopsy with 3 mm to 4 mm tumor free margins combined with supplemental cryotherapy to the remaining conjunctival margins, and alcohol corneal epitheliectomy for corneal involvement. Cryotherapy has been advocated for nearly 20 years in the treatment of PAM, as well as for supplemental treatment after excision of conjunctival melanoma. Absolute alcohol corneal epitheliectomy has been used for limbal tumors or tumors with corneal involvement, as well as for scleral treatment for more than 10 years. The aim of these supplemental treatments is to destroy clinically inapparent viable tumor cells that may persist along the margin of resection in the remaining ocular tissue. In addition, alcohol epitheliectomy allows for careful removal of involved corneal epithelial tumor after the cells are denatured, thus preventing dissemination of viable cells.

From a multivariate perspective, the risks for death as a result of conjunctival melanoma included signs and symptoms of a lump, likely reflecting large tumor size and lack of associated PAM with the melanoma on pathologic investigation. Large or thicker melanoma, whether arising in the skin or conjunctiva, carry a worse prognosis. Stefani found that tumors thicker than 1.4 mm carried a high risk for metastatic disease and death. Likewise in our study, increasing thickness of the melanoma, judged clinically or pathologically, was a risk for death. The second factor correlated with death, lack of PAM, is more difficult to understand. The relatively favorable prognosis found with conjunctival melanoma–associated PAM may be related to several factors. The flat precursor pigment of PAM may allow early detection of conjunctival melanoma. Other investigators have found a similar, better prognosis in patients with conjunctival melanoma arising from PAM whereby the 10-year survival was 86% vs 69% for those that arose de novo. However, there are reports that show no better prognosis in those patients with conjunctival melanoma with PAM. There are other factors that may explain the more favorable prognosis of conjunctival melanoma with PAM, and one of these relates to the similarity of PAM to lentigo maligna. This factor is not well understood. When reviewing the cutaneous melanoma literature, it is evident that cutaneous melanoma arising from lentigo maligna carries a better prognosis than melanoma arising de novo. Conjunctival melanoma arising in PAM resembles lentigo maligna melanoma arising in lentigo maligna, and both often affect the ocular region of the patient at the same time.

Our results should be interpreted with caution. First, the patient database may be biased toward the more advanced disease referred to an ocular oncology center, thus inappropriately weighting the incidence of recurrence, exenteration, metastasis, and death. Second, there is a tremendous amount of knowledge to be gained from investigating greater details of the histopathologic factors in this group of patients, but our goal was to analyze the available data from the standpoint of the clinician treating the patient. Often, pathologists include general information without great microscopic detail on pathology reports for the clinician to interpret. Therefore, we included only the general data that is found on most pathology reports. Third, one cannot presume that the treatment itself had significant effect on patient longevity as there may be yet unrecognized factors to explain this ef-
fect. A study designed to randomize patients to treatment groups would better address the question of the impact of treatment on recurrence, metastasis, and death. However, when one considers the rarity of conjunctival melanoma, such a study may not be feasible. Finally, with longer follow-up we expect to find increased metastases and death.

There are very few variables that we as clinicians can control regarding the management of conjunctival malignant melanoma. We cannot control the tumor quadrant location, tumor color, or symptoms of our patients. However, with astute recognition of the disease and early detection, we may be able to control the size and extent and other associated findings of the tumor. Additionally we believe that the type of surgery used for our patients may be important. We advocate, if possible, that these conjunctival malignancies be managed using a no-touch technique using wide microsurgical excisional biopsy, cryotherapy, and alcohol epitheliotomy as outlined in the literature.13 We avoid incisional biopsy for risks of local tumor dissemination and possible recurrence. It should be realized that until randomized studies regarding surgical technique for conjunctival malignancies be managed using a no-touch technique using wide microsurgical excisional biopsy, cryotherapy, and alcohol epitheliotomy as outlined in the literature.

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