CONJUNCTIVAL MELANOMA: RISK FACTORS FOR RECURRENCE, EXENTERATION, METASTASIS, AND DEATH IN 150 CONSECUTIVE PATIENTS*

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ABSTRACT

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 study group consisted of 150 consecutive patients with a diagnosis of conjunctival melanoma. 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.

Results: The Kaplan-Meier estimate 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). Ninety-eight patients (65%) had no recurrences, 28 patients (19%) had 1, 11 patients (7%) had 2, 5 patients (3%) had 3, and 8 patients (5%) had 4 or more recurrences. According to multivariate analysis, the factors that predicted local tumor recurrence were the location of the melanoma (not touching the limbus) (P = .01) and tumor-margin pathology (lateral margin involved) (P = .02). Multivariate analysis for features predictive of ultimate exenteration included initial visual acuity (20/40 or worse) (P = .0007), melanoma color (red) (P = .01), and melanoma location (not touching the limbus) (P = .02).

Tumor metastasis occurred in 16% of patients at 5 years, 26% at 10 years, and 32% at 15 years. Metastasis was initially in the regional lymph nodes in 17 cases, brain in 4, liver in 3, lung in 2, and disseminated in 1 case. Risks for metastases with use of multivariate analysis included tumor-margin pathology (lateral margin involved) (P = .002) and melanoma location (not touching limbus) (P = .04).

Tumor-related death occurred in 7% of patients at 5 years and 13% at 8 years. Risk factors for death with use of multivariate analysis included initial symptoms (lump) (P = .004) and pathologic findings (de novo melanoma without primary acquired melanosis) (P = .05).

In a series of univariate analyses, 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). Patients who were managed with excisional biopsy using the "no-touch technique" plus alcohol corneal epitheliectomy and supplemental cryotherapy fared far better than those treated with excisional biopsy alone. In addition, the surgical technique used before referral to us was critical. Those patients who had an incisional diagnostic biopsy prior to referral were at risk for more than 1 recurrence (P = .04), and those who had excisional biopsy alone without supplemental cryotherapy were at risk for eventual exenteration (P =.0006) and death (P = .04).

Conclusions: Conjunctival malignant melanoma is a potentially deadly tumor. In this study, metastasis was detected in 26% of patients and death occurs in 13% at 10 years. The surgical technique of tumor management was found to be possibly related to tumor metastases and death. Meticulous surgical planning, use of wide microsurgical excisional biopsy with the no-touch technique, and supplemental alcohol corneal epitheliectomy and conjunctival cryotherapy performed by experienced surgeons are advised. Incisional biopsy should be avoided.

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INTRODUCTION

Malignant melanoma is a potentially fatal tumor that arises from melanocytes, most often in the sun-exposed skin.[1] Less commonly, melanoma originates from other tissues, such as the uvea and the mucous membranes, including the vulva, rectum, mouth, respiratory tract, and conjunctiva. Conjunctival melanoma represents only 1.6% of all noncutaneous melanoma.[2] In 1987, the Swedish National Cancer Registry filed 1,243 new cases of cutaneous melanoma in a population of 8.4 million.[3] That year, 70 new cases of uveal melanoma and only 2 new cases of conjunctival melanoma were reported from the same population in Sweden. This

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highlights the rarity of conjunctival melanoma.

Several reports on conjunctival melanoma have been published, generally emanating from pathology laboratories or national cancer registries.[4-14] These reports have primarily addressed the microscopic features of conjunctival melanoma and analyzed the effects of these features on patient outcome. The pathologic factors recognized to be predictive of patient death from conjunctival melanoma include increasing tumor thickness; involvement of the palpebral, caruncular, or forniceal conjunctiva; mixed-cell type; lymphatic invasion; and increasing mitotic activity. In addition, those tumors with associated primary acquired melanosis that demonstrated pagetoid growth pattern, atypical melanocytes, full-thickness epithelial involvement, and absence of inflammatory response have carried a worse prognosis.[6,9,13,14] Most previous 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 reports 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 primary acquired melanosis, and many other important clinical features have not been addressed. In addition to the lack of clinical details, there is a lack of information about the surgical approach to these tumors. According to most previous reports, there have been many clinicians using various surgical techniques for tumor management, and little, if any, of this vital information has been included in the analysis on 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. Some portions of the treatment of conjunctival melanoma are based on concepts learned from dermatologic management of the more common cutaneous malignant melanoma.[15] The techniques for surgical management of this rare tumor have slowly evolved. Most of the techniques arise from years of shared experience[16-20] in major ocular oncology centers that handle conjunctival and other ocular tumors.

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

PATIENTS AND METHODS

The records of all patients given the diagnosis of conjunctival melanoma between April 1974 and September 1997 were identified and included in this analysis. Each case was analyzed according to specific clinical and pathologic features. The variables marked with a dagger symbol (†) in the following paragraphs were used as references in the univariate and multivariate analysis.

Clinical variables included patient age, race (white,† black), sex (male,† female), eye (OD,† OS), signs and symptoms (spot,† lump, irritation, other, none), past medical history (cutaneous melanoma, dysplastic nevus syndrome, uveal melanoma, neurofibromatosis, acquired immune deficiency syndrome, others), family history (conjunctival melanoma, cutaneous melanoma, dysplastic nevus syndrome, uveal melanoma, neurofibromatosis, others), cutaneous complexion (fair white,† olive white, nonwhite), and previous systemic treatment (chemotherapy, corticosteroids, ocular radiation). Previous management of the tumor (before referral) was assessed for type of surgical technique (incisional biopsy, excisional biopsy,† cryotherapy, alcohol corneal epitheliectomy) and number of prior recurrences. General ocular clinical features included visual acuity, iris color (blue,† green, brown), eyelid lentigo maligna (present, absent†), and associated primary acquired melanosis and its extent (number of clock hours involved). Tumor features at initial presentation included quadrant location of melanoma (superior, nasal, inferior, lateral,† diffuse), anatomic conjunctival location of melanoma (bulbar,† fornix, tarsus, plica semilunaris, caruncle), bulbar extension of melanoma (number of clock hours involved), proximity of melanoma to limbus (millimeters), radial corneal involvement by melanoma (millimeters), and depth of corneal involvement by melanoma (epithelium,† stroma, Descemet's membrane).

Additional clinical tumor features included melanoma base size (millimeters), melanoma thickness (millimeters), melanoma color (brown,† red, yellow, variable), melanoma feeder vessels (present, absent†), initial tumor surgery after referral (incisional biopsy, excisional biopsy,† cryotherapy, alcohol corneal epitheliectomy, exenteration), local recurrence of melanoma (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 previous surgical treatment. The site of recurrence could be the same as, or different from, that of previous tumors. Histopathologically proven melanoma metastasis and melanoma-related death were recorded.

Histopathologic data were recorded from pathology reports submitted to the clinician on the clinical chart. The features analyzed included melanoma thickness by gross examination (millimeters), melanoma surgical margins by microscopic examination (base involved, lateral margin involved, margins clear†), and associated microscopic features (nevus, primary acquired melanosis, none†).

STATISTICAL ANALYSIS

The clinical and histopathologic parameters were analyzed in a nonrandomized fashion as they impacted on 4 end points: local melanoma recurrence, orbital exenteration, melanoma metastases, and melanoma-related death. Melanoma recurrence was defined as the development of a new tumor, histopathologically confirmed to be 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 reappearance 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 presentation, number of recurrences before referral, initial visual acuity, proximity of melanoma to the corneoscleral limbus, melanoma radial corneal involvement, melanoma base and thickness, total number of local melanoma recurrences, and tumor thickness by gross histopathologic examination, which were analyzed as continuous variables and later grouped into discrete categories to derive cut-off values. In addition, clock-hour extension of primary acquired melanosis 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 univariable level to determine an independent set of predictors for each outcome. Subsequent multivariable models simultaneously fitted the set of independent predictors and tested other biologically important variables for inclusion in the final multivariable model. Kaplan-Meier survival estimates of the probability of recurrence, orbital exenteration, metastasis, and death as a function of time were performed.[21]

RESULTS

Over a 23-year period, from April 1974 to September 1997, 254 conjunctival malignant melanomas in 150 patients were evaluated. The mean follow-up provided after referral to an ocular oncology center was 4.2 years (range, 1 month to 20.2 years). The mean overall patient follow-up provided by an ocular oncology center along with the referring physician was 7 years (range, 1 month to 35.3 years).

The mean age at presentation was 60 years (median, 62 years; range, 16 to 89 years). At presentation, 2 patients (1%) were under 20 years of age, 18 (12%) were 21 to 40 years, 49 (33%) were 41 to 60 years, and 80 (54%) were older than 60 years. All patients were white except for 1 African American. The skin complexion of the white patients was judged light (fair) in 148 (99%) and dark (olive) in 1 (1%). There were 75 male (50%) and 75 female (50%) patients. In all cases, the disease was unilateral. The right eye was involved in 67 patients (45%) and the left eye in 83 (55%). The main symptoms noted by patients were a spot in 116 (77%), a lump in 26 (17%), ocular irritation in 2 (1%), and others (eg, pain) in 1 (1%). Three patients (2%) did not report any symptoms, and information about signs and symptoms was not available in 2 cases (1%).

Preexisting systemic disease, including neurofibromatosis, was present in 1 patient (1%), cutaneous melanoma in 7 patients (5%), and dysplastic nevus syndrome in 2 (1%); none of the patients had uveal melanoma or acquired immunodeficiency syndrome. The cutaneous melanoma was located on the eyelid in 3 patients, back in 2, cheek in 1, and hand in 1 patient. Lentigo maliga of the eyelid was present in 8 patients (5%). Two patients (1%) had a family history of cutaneous melanoma, and 1 patient (1%) a family history of uveal melanoma. None of the patients had a family history of dysplastic nevus syndrome or conjunctival melanoma. Previous treatments included systemic chemotherapy for other cancers in 1 (1%); no patients had had systemic corticosteroid treatment or ocular radiotherapy.

Prior to referral, tumor management elsewhere included incisional biopsy in 20 cases (13%); excisional biopsy in 57 (38%); excisional biopsy and cryotherapy in 14 (9%); and excisional biopsy, cryotherapy, and alcohol corneal epitheliectomy in 2 (1%); 55 patients (38%) had not had any treatment. Prior to referral, 34 patients (23%) had had 1 recurrence, 2 patients (2%) 2 recurrences, 3 patients (3%) 3 recurrences, 1 patient (1%) 4 recurrences, 1 patient (1%) 7 recurrences, 1 patient (1%) 11 recurrences, and 1 patient (1%) 16 recurrences. In 107 patients (71%), there were no recurrences prior to referral.

Initial visual acuity was 6/6 in 87 patients (58%), 6/7.5 in 18 (12%), 6/9 in 15 (10%), 6/12 in 8 (5%), 6/15 in 7 (6%), 6/21 in 3 (2%), and 6/24 or worse in 12 (8%). The iris color was blue in 47 eyes (31%), green in 17 (11%), brown in 85 (57%), and not specified in 1 (1%). Ipsilateral conjunctival primary acquired melanosis was present in 67 patients (45%); the extent of involvement was less than 3 clock hours in 19 (13%), 4 to 6 clock hours in 27 (18%), 7 to 9 clock hours in 10 (7%), and 10 to 12 clock hours in 11 (7%).

The location of melanoma was classified as superior in 24 patients (16%), medial in 26 (17%), inferior in 33 (22%), lateral in 63 (42%), and diffuse in 4 (3%). The location of the tumor epicenter was bulbar in 138 (92%), fornix in 4 (3%), palpebral in 6 (4%), plica semilunaris in 1 (1%), and caruncle in 1 (1%) (Fig 1). The extent of melanoma was 1 clock hour or less in 18 patients (12%), 2 clock hours

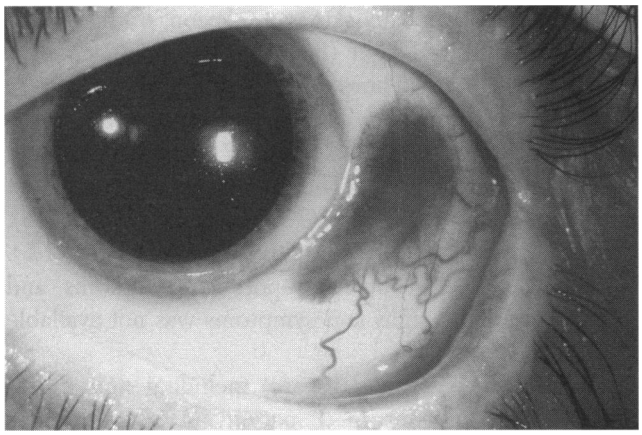

FIGURE 1A
Clinical appearance of conjunctival melanoma. Pigmented conjunctival melanoma at corneoscleral limbus.

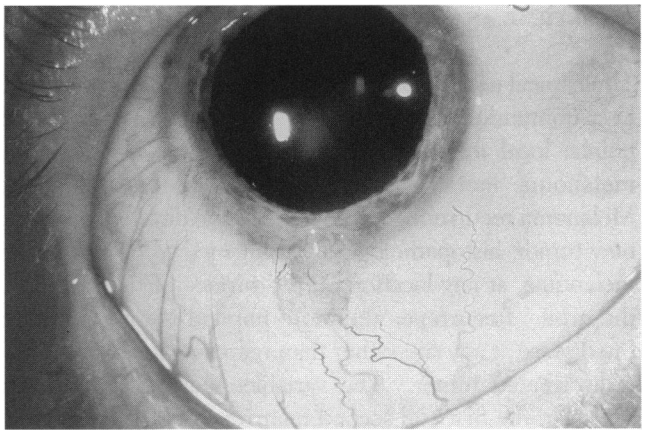

FIGURE 1B
Clinical appearance of conjunctival melanoma. Nonpigmented recurrent conjunctival melanoma at corneoscleral limbus.

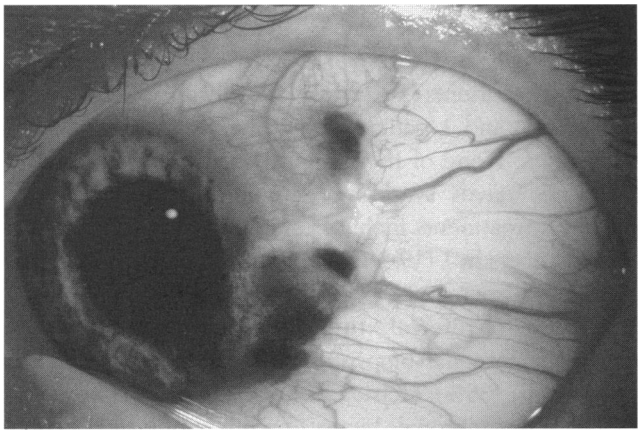

FIGURE 2A
Surgical treatment of conjunctival melanoma. Before surgery, tumor extends from 12:30- to 5:00-o'clock position at limbus and involves corneal epithelium.

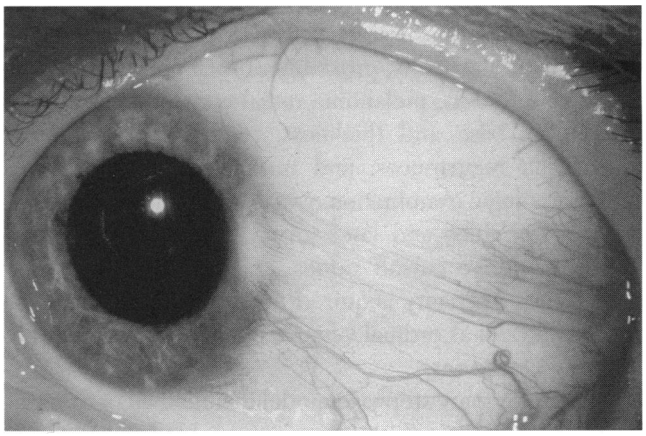

FIGURE 2B
Surgical treatment of conjunctival melanoma. After surgery (alcohol corneal epitheliectomy and excisional biopsy using "no-touch" technique and supplemental cryotherapy), conjunctival surface has healed well with no tumor recurrence over 10-year follow-up. Note mild dragging of conjunctival tissue at resection site.

in 61 (41%), 3 clock hours in 37 (25%), 4 clock hours in 13 (9%), 5 clock hours in 7 (5%), and 6 or more clock hours in 7 (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 to 8 mm). The tumor touched the limbus in 91 eyes (61%) and did not reach the limbus in 56 (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 to 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 the initial visit.

The mean tumor base from a clinical standpoint was 8 mm (median, 8 mm; range, 2 to 20 mm), and the mean tumor thickness was 2 mm (median, 2 mm; range, 1 to 15 mm). The melanoma was classified as brown in 102 patients (68%), red in 16 (11%), yellow in 29 (19%), and a combination of brown and yellow in 3 (2%). Tumor feeder vessels were present in 59 (39%) and absent in 91 (61%).

The initial surgical approach to the tumor after referral to us was excisional biopsy alone in 27 patients (18%); excisional biopsy and cryotherapy in 46 (31%); excisional biopsy, cryotherapy, and alcohol corneal epitheliectomy in 65 (43%) (Fig 2); orbital exenteration in 7 (5%); and observation in 5 (3%); incisional biopsy was not used in any patients. Orbital exenteration was eventually performed in 20 patients (13%). Final visual acuity in the involved eye after all treatments at last follow-up was 6/6 in 532 patients (35%), 6/7.5 in 26 (17%), 6/9 in 14 (9%), 6/12 in 9 (6%), 6/15 in 8 (5%), 6/21 in 1 (1%), 6/24 in 1 (1%), 6/30 in 3 (2%), 6/60 in 5 (3%) and 6/120 or worse

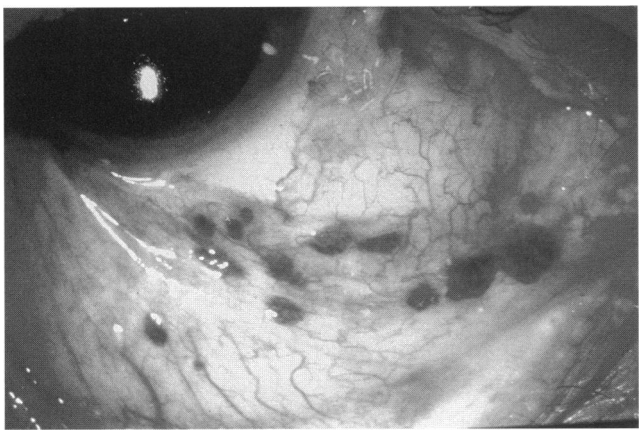

FIGURE 3A
Recurrent conjunctival melanoma. Multiple pigmented recurrent tumors are noted along bulbar conjunctival fold in patient who had had biopsy at another hospital several months earlier.

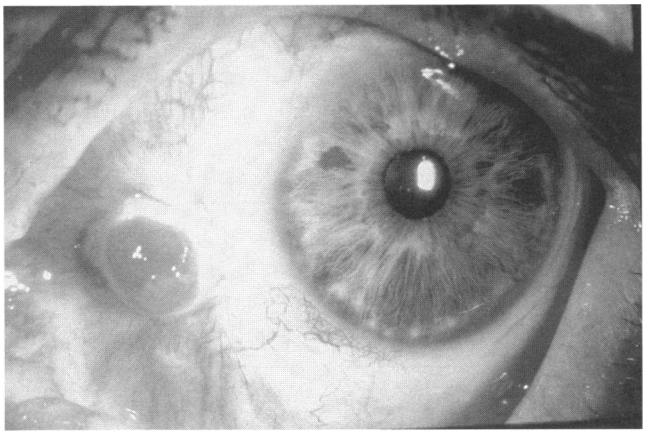

FIGURE 3B
Recurrent conjunctival melanoma. Amelanotic extralimbal recurrence in patient who had several previous excisional biopsies of conjunctival melanoma.

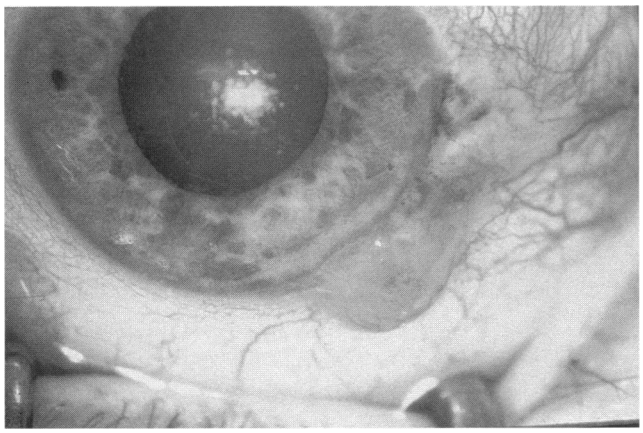

FIGURE 4A
Scleral invasion by conjunctival melanoma. Amelanotic conjunctival melanoma and adjacent primary acquired melanosis at corneoscleral limbus.

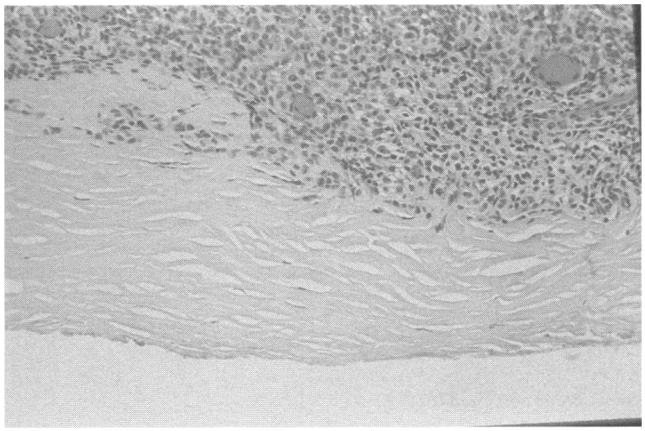

FIGURE 4B
Scleral invasion by conjunctival melanoma. Excisional biopsy with thin lamella of underlying sclera was performed and melanoma was found infiltrating superficial sclera, sparing deep margin. There was no recurrence over 11-year follow-up.

(including 20 exenteration patients) in 30 (20%).

On histopathologic examination, the mean gross tumor thickness was 2 mm (median, 2 mm; range, 1 to 12 mm). By report, the surgical margins were judged clear of tumor in 89 cases (59%); the lateral margin was involved with tumor in 11 (7%) cases, the base was involved in 13 (9%), both lateral and base were involved in 4 (3%), and margins were not specified in 33 cases (22%). In addition to the conjunctival melanoma, there was an associated conjunctival nevus in 6 cases (4%) and primary acquired melanosis in 80 (53%); associated lesions were not present in 55 cases (37%) and not specified in 9 (6%).

END POINTS

Results related to the 4 end points of tumor recurrence, orbital exenteration, tumor metastasis, and patient death are discussed below.

Recurrence

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

According to Kaplan-Meier survival estimates, recurrence was detected in 26% of patients at 5 years, 51% at 10 years, and 65% at 15 years follow-up (Fig 5). The mean interval from first recurrence to second recurrence would be 15 months (median, 9 months; range, 1 to 49 months), and the mean interval from second recurrence to third

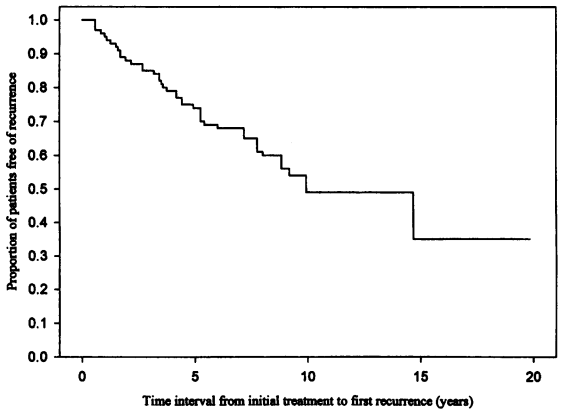

FIGURE 5
Kaplan-Meier estimates of patients free of tumor recurrence.

recurrence, 15 months (median, 15 months; range, 1 to 41 months).

In a series of univariate analyses, the factors predictive of recurrence of conjunctival melanoma included melanoma not touching the limbus (P = .001), melanoma 2 mm or more from the limbus (P =.001), extent of primary acquired melanosis for 7 to 9 clock hours (P = .003), melanoma color (red) (P = .004), gross tumor thickness on pathologic examination 4 mm or more (P = .02), melanoma located in the superior quadrant (P = .02), lateral and base margins of specimen involved with tumor on pathologic examination (P = .03), and corneal involvement with melanoma 2 mm or more (P = .04) (Table I). According to univariate analysis, the risk for second recurrence of melanoma included melanoma not touching the

TABLE I: UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RECURRENCE IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Age (yr) [n=149]					
<50†	26	16			
≥50	71	36	.89	1.0	[0.6,1.9]
Sex [n=149]					
Male†	50	25			
Female	47	27	.49	0.8	[0.5,1.4]
Eye [n=149]					
OD†	45	22			
OS	52	30	.74	0.9	[0.5,1.6]
Signs/symptoms [n=148]					
None	3	0			
Spot†	77	39			
Lump	15	11	.34	1.4	[0.7,2.7]
Irritation*	2	0			
Other*	0	1			
Prior surgery before referral [n=137]					
None	31	13	.50	0.8	[0.4,1.6]
Incision	12	8	.26	1.6	[0.7,3.7]
Excision†	35	22			
Excision,cryotherapy	8	6	.59	0.8	[0.3,1.9]
Excision,cryotherapy,alcohol*	2	0			
Prior number of recurrence before referral [n=149]			.32	1.1	[1.0,1.2]
0	72	34			
1	22	12			
2	0	2			
≥3	3	4			
Visual acuity (initial) [n=149]			.33	1.0	[1.0,1.1]
20/20-20/30†	78	41			
20/40-20/100	13	6	.12	2.0	[0.8,4.9]
20/200-light perception	6	5	.53	1.3	[0.5,3.4]
Iris color [n=149]					
Blue†	27	19			
Green	13	4	.13	0.43	[0.1,1.3]
Brown	56	29	.30	0.7	[0.4,1.3]
Lentigo maligna eyelid [n=147]					
Yes	3	5	.75	1.2	[0.5,2.9]
No†	92	47			

TABLE 1 (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RECURRENCE IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Primary acquired melanosis extension (clock hours) [n=66]					
1-3†	15	4			
4-6	18	8	.09	2.9	[0.8,10.5]
7-9	5	5	.003‡	9.0	[2.1,38.8]
10-12	8	3	.36	2.0	[0.4,9.0]
Melanoma quadrant [n=149]					
Superior	8	15	.02‡	2.2	[1.1,4.4]
Medial	18	8	.54	1.3	[0.6,3.0]
Inferior	23	10	.49	1.3	[0.6,2.8]
Lateral†	44	19			
Diffuse°	4	0			
Melanoma epicenter anatomic location [n=149]					
Bulbar conjunctiva†	89	48			
Fornix conjunctiva	4	0	.36	NA	NA
Palpebral conjunctiva	3	3	.33	1.9	[0.6,6.1]
Plica semilunaris	1	0			
Caruncle	0	1			
Melanoma bulbar extension (clock hours) [n=145]			.64‖	0.9	[0.8,1.1]
no bulbar tumor	2	1			
1-3†	76	39			
4-6	12	9	.60	1.2	[0.6,2.5]
7-9	1	0	.61	0.6	[0.1,4.3]
10-12	4	1			
Melanoma touch limbus [n=146]					
Yes†	64	26			
No	31	25	.001§	2.5	[1.4,4.6]
Melanoma proximity to limbus (mm) [n=146]					
0	65	24			
1	2	2			
2	5	3			
≥3	23	22	.001§	1.2	[1.1,1.3]
Melanoma proximity to limbus (mm) [n=146]					
<2mm†	67	26			
≥2mm	28	25	.001§	2.6	[1.5,4.6]
Melanoma radial corneal involvement (mm) [n=149]					
0	42	27			
1	11	6			
2	15	8			
≥3	29	11	.05	0.8	[0.7,1.0]
Melanoma radial corneal involvement (mm) [n=149]					
<2mm†	53	33			
≥2mm	44	19	.04§	1.8	[1.1,3.2]
Melanoma tumor base (mm) [n=142]					
<8mm†	41	19			
≥8mm	51	31	.93	1.03	[0.6,1.8]
Melanoma tumor thickness (mm) [n=142]					
<3 mm†	70	31			
≥3mm	22	19	.12	1.6	[0.9,2.8]
Melanoma color [n=149]					
Brown†	67	35			
Red	7	8	.004§	3.2	[1.4,7.1]
Yellow	20	9	.97	0.9	[0.4,2.1]
Variable°	3	0			

TABLE I (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RECURRENCE IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Melanoma feeder vessel [n=148]					
Yes	37	20	.96	1.0	[0.6,1.7]
No†	60	31			
Melanoma initial surgery after referral [n=144]					
Incision°	0	0			
Excision†	13	14			
Excision,cryotherapy	23	22	.94	1.0	[0.5,2.0]
Excision,cryotherapy,alcohol	50	15	.07	0.5	[0.2,1.1]
Exenteration	6	1	.5	0.5	[0.1,4.0]
Pathology tumor thickness (gross) [n=123]			.02‡	1.1	[1.0,1.3]
<1	7	1			
1	26	10			
2	24	11			
≥3	24	20			
Pathology tumor thickness (gross) [n=115]					
<4mm†	60	29			
≥4mm	14	12	.02‡	2.3	[1.1,4.5]
Pathology tumor margins (microscopic) [n=116]					
Lateral involved	5	6	.05	2.5	[1.0,6.1]
Base involved	9	4	.55	1.3	[0.5,4.0]
Both lateral and base involved	1	3	.03	3.8	[1.1,12.8]
Margins clear†	61	27			
Pathology associated features with melanoma [n=140]					
Nevus	29	26	.11	0.6	[0.4,1.1]
Primary acquired melanosis	55	24	.6	0.7	[0.1,2.9]
None†	4	2			

S, significant; NS, not significant; NA, not applicable.
° Not analyzed (too few events).
† Reference variable (see text).
‡ $P < .05$.
§ $P < .01$.
‖ Ordinal.

limbus ($P = .004$), primary acquired melanosis 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 in the superior quadrant ($P = .02$).

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 II). In a second multivariate model, the significant variables were melanoma location not touching the limbus ($P = .001$) and tumor color red ($P = .01$). With use of multivariate analyses, the only risk for second tumor recurrence was melanoma 2 mm for more from the limbus ($P = .02$).

Orbital Exenteration

Of the 150 patients, 20 (13%) were eventually treated with orbital exenteration during the course of this study. Of the 20 exenterations, 7 were performed at the initial surgery, 6 after first recurrence was detected, 3 after second recurrence, 2 after third recurrence, and 2 after 4 or more recurrences. According to Kaplan-Meier survival estimates, exenteration were performed in 8% of patients by 5 years, 16% by 10 years, and 32% by 15 years follow-up (Fig 6).

By univariate analyses, the risks for eventual orbital exenteration included visual acuity of 20/40 to 20/100 ($P = .0002$), tumor thickness 4 mm or more on pathologic examination ($P = .005$), corneal involvement with melanoma 2 mm or more ($P = .002$), melanoma in inferior quadrant ($P = .003$) or superior quadrant ($P = .04$), melanoma not touching limbus ($P = .005$), surgery before referral consisting of excisional biopsy alone without adjuvant cryotherapy ($P = .006$), pathologic examination showing de novo origin of the

TABLE II: MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF FIRST LOCAL TUMOR RECURRENCE IN 150 PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Melanoma touch limbus (yes† versus no)	0.01°	2.3	[1.2,4.6]
Pathology tumor margins (lateral margin involved versus base involved, lateral and base involved, and margins clear)	0.02°	2.9	[1.2, 7.1]

° $P<.05$.
† Reference variable (see text).

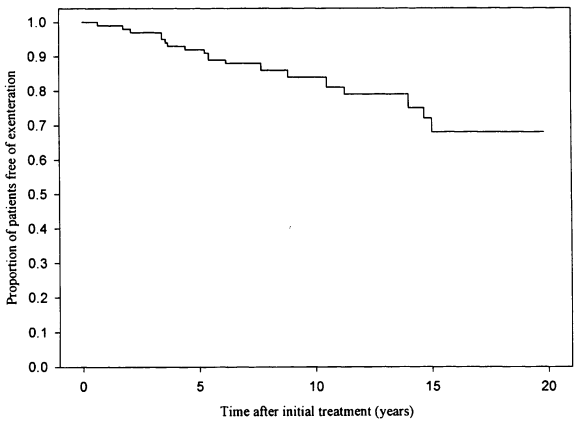

FIGURE 6
Kaplan-Meier estimates of patients free of exenteration.

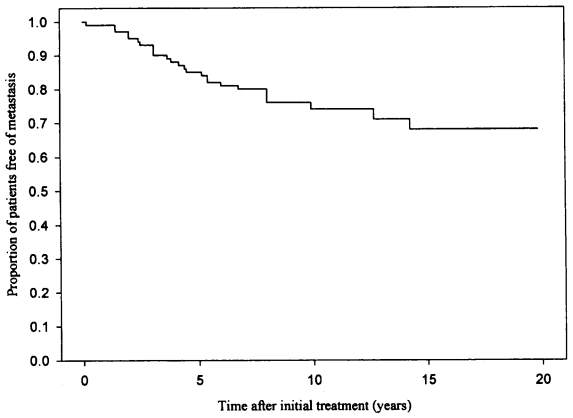

FIGURE 7
Kaplan-Meier estimates of patients free of tumor metastasis.

tumor (P = .02), melanoma located in the fornix (P =.02), and signs or symptoms of lump (P =.03) (Table III).

According to multivariate analysis, the risks for eventual orbital exenteration included initial visual acuity 20/40 to 20/100 (P = .0007) or 20/200 or worse (P = .01), visual acuity 20/20 to 20/40, melanoma color red (P =.01), and melanoma not touching the limbus (P =.02) (Table IV).

Metastasis

Of the 150 patients, 27 (18%) eventually developed metastasis. According to Kaplan-Meier survival estimates, metastasis was detected in 16% of patients by 5 years, 26% by 10 years, and 32% by 15 years of follow-up (Fig 7). The location of the first detectable metastasis would be facial lymph nodes in 17 patients, lung in 2, brain in 4,

TABLE III: UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON EVENTUAL ORBITAL EXENTERATION IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Age (yr) [n=149]					
<50†	37	5			
>50	92	15	0.69	1.2	[0.5,3.4]
Sex [n=150]					
Male†	69	6			
Female	61	14	0.22	1.8	[0.7,4.8]
Eye [n=150]					
OD†	59	8			
OS	71	12	0.85	0.9	[0.4,2.2]
Signs/symptoms [n=148]					
None°	3	0			
Spot†	104	12			
Lump	19	7	0.03‡	2.8	[1.1,7.1]
Irritation°	2	0			
Other°	1	0			

TABLE III (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON EVENTUAL ORBITAL EXENTERATION IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Prior surgery before referral [n=137]					
None	41	3	0.14	0.4	[0.11,1.4]
Incision	15	5	0.40	1.6	[0.5,4.5]
Excision†	43	12			
Excision,cryotherapy	14	0	0.006§‖		
Excision,cryotherapy,alcohol°	2	0			
Prior number of recurrences before referral [n=149]			0.40	1.1	[0.9,1.2]
0	96	10			
1	27	7			
2	1	1			
≥3	5	2			
Visual acuity (initial) [n=150]			0.003§	1.2	[1.1,1.3]
20/20-20/30†	109	11			
20/40-20/100	13	6	0.0002§	7.5	[2.6,21.1]
20/200-light perception	8	3	0.06	3.4	[0.9,12.2]]
Iris color [n=149]					
Blue†	41	6			
Green	15	2	0.85	0.85	[0.17,4.3]
Brown	73	12	0.96	1.0	[0.4,2.7]
Lentigo maligna eyelid [n=147]					
Yes	6	2	0.83	0.85	[0.2,3.7]
No†	121	18			
Primary acquired melanosis extension (clock hours) [n=67]					
1-3†	18	1			
4-6	24	3	0.34	3.0	[0.3,29.1]
7-9	9	1	0.26	5.4	[0.3,103.9]
10-12	10	1	0.36	3.8	[0.2,68.0]
Melanoma quadrant [n=150]					
Superior	18	6	0.04‡	4.4	[1.1,17.7]
Medial	24	2	0.61	1.5	[0.3,9.5]
Inferior	25	8	0.003§	7.5	[2.0,29.3]
Lateral†	60	3			
Diffuse°	3	1			
Melanoma epicenter anatomic location [n=150]					
Bulbar conjunctiva†	121	16			
Fornix conjunctiva	3	1	0.02°	13.4	[1.6,111.9]
Palpebral conjunctiva	4	2	0.14	3.1	[0.7,13.3]
Plica semilunaris°	1	0			
Caruncle°	1	0			
Melanoma bulbar extension (clock hours) [n=142]			0.12	1.1	[01.0,1.4]
1-3†	103	13			
4-6	19	2			
7-9	1	0			
10-12	3	2			
Melanoma touch limbus [n=147]					
Yes†	84	7			
No	44	12	0.005§	3.8	[1.5,9.8]
Melanoma proximity to limbus (mm) [n=147]			0.06	1.2	[1.0,1.4]
0	81	9			
1	4	0			
2	7	1			
≥3	36	9			
Melanoma proximity to limbus (mm) [n=147]					
<2mm†	85	9			
>2mm	43	10	0.06	2.3	[1.0,5.8]

TABLE III (CONTINUED: UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON EVENTUAL ORBITAL EXENTERATION IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO RECURRENCE (N=98)	RECURRENCE (N=52)	*P VALUE*	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Melanoma radial corneal involvement (mm) [n=150]			0.04‡	1.7	[1.1,2.5]
0	54	15			
1	16	1			
2	24	0			
≥3	36	4			
Melanoma radial corneal involvement (mm) [n=150]					
<2mm†	70	16			
≥2mm	60	4	0.002‡	3.8	[1.3,11.4]
Melanoma tumor base (mm) [n=143]					
<8mm†	54	7			
≥8mm	69	13	0.54	1.3	[0.5,3.3]
Melanoma tumor thickness (mm) [n=143]					
<3mm†	90	12			
≥3mm	33	8	0.30	1.6	[0.7,4.0]
Melanoma color [n=150]					
Brown†	90	12			
Red	13	3	0.05	3.5	[0.9,12.7]
Yellow	25	4	0.50	1.5	[0.5,4.6]
Variable*	2	1			
Melanoma feeder vessel [n=149]					
Yes	52	6	0.30	0.6	[0.2,1.6]
No†	77	14			
Melanoma initial surgery after referral [n=145]					
Incision*	0	0			
Excision†	23	4			
Excision,cryotherapy	42	4	0.81	0.8	[0.2,3.5]
Excision,cryotherapy,alcohol	60	5	0.89	1.1	[0.3,4.3]
Exenteration	0	7	NA		
Local melanoma recurrence (total number) [n=149]			0.40	1.1	[0.9,1.3]
0	96	7			
1	17	5			
2	8	3			
≥3	8	5			
Pathology tumor thickness (gross) [n=124]			0.0009§	1.3	[1.1,1.5]
<1	7	1			
1	32	4			
2	34	2			
≥3	37	7			
Pathology tumor thickness (gross) [n=116]					
<4mm†	83	7			
≥4mm	20	6	0.005§	5.2	[1.7,16.5]
Pathology tumor margins (microscopic) [n=117]					
Lateral involved	9	2	0.08	4.6	[0.8,25.8]
Base involved	11	2	0.06	5.7	[0.9,34.3]
Both lateral and base involved	3	1	0.06	8.6	[0.9,83.8]
Margins clear†	83	6			
Pathology associated features with melanoma [n=141]					
Nevus	6	0	0.09	‖	
Primary acquired melanosis†	75	5			
None	40	15	0.02‡	3.5	[1.2,9.5]

NA, Not applicable; NS, Not significant; S, Significant
* Not analyzed (too few events).
† Reference variable (see text)
‡ $P<.05$.
§ $P<.01$.
‖ No risk ratio can be calculated owing to cell with no events.

TABLE IV. MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF EVENTUAL ORBITAL EXENTERATION IN 150 PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	*P* VALUE	RELATIVE RISK	CONFIDENCE INTERVAL [95%]
Initial visual acuity (20/20-20/30† versus 20/40-20/100)	.0007°°	8.1	[2.4,27.5]
Initial visual acuity (20/20-20/30† versus 20/200 or worse)	.01‡	5.8	[1.4,22.2]
Melanoma color (brown† versus red)	.01‡	6.0	[1.5,24.0]
Melanoma touch limbus (yes† versus no)	.02‡	3.3	[1.1,9,9]

° $P<.01$
† Reference variable
‡ $P<.05$

TABLE V: UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR METASTASIS IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO METASTASIS (N=128)	METASTASIS (N=27)	*P* VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Age (yr) [n=149]					
<50	34	8			
≥50†	88	19	0.87	1.1	[0.5,2.5]
Sex [n=150]					
Male†	60	15			
Female	63	12	0.25	0.7	[0.3,1.4]
Eye [n=150]					
OD†	51	16			
OS	72	11	0.04‡	0.4	[0.2,0.9]
Signs/symptoms [n=148]					
None°	2	1			
Spot†	99	17			
Lump	18	8	0.08	2.1	[0.9,5.0]
Irritation°	2	0			
Other°	1	0			
Prior surgery before referral [n=137]					
None	40	4	0.15	0.4	[0.1,1.4]
Incision	16	4	0.67	1.2	[0.4,4.0]
Excision†	44	13			
Excision,cryotherapy	11	3	0.54	0.7	[0.2,2.4]
Excision,cryotherapy,alcohol°	2	0			
Prior number of recurrences before referral [n=149]			0.56	0.9	[0.7,1.2]
0	91	15			
1	24	10			
2	1	1			
≥3	6	1			
Visual acuity (initial) [n=150]			0.56	1.0	[0.9,1.2]
20/20-20/30†	99	21			
20/40-20/100	16	3	0.34	1.6	[0.6,3.9]
20/200-light perception	8	3	0.81	1.3	[0.2,9.6]
Iris color [n=149]					
Blue†	36	11			
Green	15	2	0.30	0.4	[0.1,2.0]
Brown	71	14	0.32	0.7	[0.3,1.5]
Lentigo maligna eyelid [n=147]					
Yes	6	2	0.70	0.7	[0.2,3.1]
No†	114	25			
Primary acquired melanosis extension (clock hours) [n=67]			0.60	1.2	[0.6,2.3]
1-3†	18	1			
4-6	21	6			
7-9	10	0			
10-12	10	1			

TABLE V (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR METASTASIS IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO METASTASIS (N=123)	METASTASIS (N=27)	*P* VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Melanoma quadrant [n=150]					
Superior	16	8	0.02‡	3.7	[1.2,11.3]
Medial	24	2	0.98	1.0	[0.2,5.3]
Inferior	21	12	0.0009§	6.0	[2.1,17.3]
Lateral†	58	5			
Diffuse	4	0			
Melanoma epicenter anatomic location [n=150]					
Bulbar conjunctiva†	114	24			
Fornix conjunctiva	3	1	0.11	5.2	[0.7,40.0]
Palpebral conjunctiva	4	2	0.40	1.9	[0.4,8.0]
Plica semilunaris*	1	0			
Caruncle*	1	0			
Melanoma bulbar extension (clock hours) [n=143]			0.80	1.0	[0.9,1.2]
1-3†	98	18			
4-6	15	6			
7-9	1	0			
10-12	4	1			
Melanoma touch limbus [n=147]					
Yes†	80	11			
No	42	14	0.01‡	2.8	[1.3,6.4]
Melanoma proximity to limbus (mm) [n=147]			0.02‡	1.2	[1.0,1.4]
0	77	13			
1	4	0			
2	7	1			
≥3	32	13			
Melanoma proximity to limbus (mm) [n=147]					
<2mm†	81	13			
≥2mm	39	14	0.03‡	2.4	[1.1,5.1]
Melanoma radial corneal involvement (mm) [n=150]			0.30	0.9	[0.7,1.1]
0	52	17			
1	16	1			
2	21	3			
≥3	34	6			
Melanoma radial corneal involvement (mm) [n=150]					
<2mm†	68	18			
≥2mm	55	9	0.13	1.9	[0.8,4.1]
Melanoma tumor base (mm) [n=143]					
<8mm†	53	8			
≥8mm	64	18	0.26	1.6	[0.7,3.7]
Melanoma tumor thickness (mm) [n=143]					
<3mm†	85	17			
≥3mm	32	9	0.59	1.3	[0.6,2.8]
Melanoma color [n=150]					
Brown†	84	18			
Red	12	4	0.05	3.0	[1.0,9.0]
Yellow	24	5	0.80	1.2	[0.4,3.1]
Variable*	3	0			
Melanoma feeder vessel [n=149]					
Yes	50	8	0.32	0.7	[0.3,1.5]
No†	72	19			
Melanoma initial surgery after referral [n=145]					
Incision*	0	0			
Excision†	16	11			
Excision,cryotherapy	39	7	0.06	0.4	[0.1,1.0]
Excision,cryotherapy,alcohol	58	7	0.03‡	0.3	[0.1,0.9]
Exenteration	6	1	0.90	0.8	[0.1,6.5]

TABLE V (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR METASTASIS IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO METASTASIS (N=123)	METASTASIS (N=27)	P VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Local melanoma recurrence					
(total number) [n=149]			0.43	1.1	[0.9,1.3]
0	92	11			
1	17	5			
2	5	6			
≥3	8	5			
Pathology tumor thickness (gross) [n=124]			0.80	1.0	[0.8,1.2]
<1	5	3			
1	31	5			
2	31	5			
≥3	36	8			
Pathology tumor thickness (gross) [n=116]					
<4mm†	77	13			
≥4mm	21	5	0.31	1.7	[0.6,4.8]
Pathology tumor margins (microscopic) [n=117]					
Lateral involved	6	5	0.002§	5.8	[1.9,17.5]
Base involved	10	3	0.15	2.7	[0.7,10.0]
Both lateral and base involved	2	2	0.02‡	6.3	[1.3,29.4]
Margins clear†	80	9			
Pathology associated features with melanoma [n=141]					
Nevus	5	1	0.70	0.6	[0.1,4.8]
Primary acquired melanosis	71	9	0.05	0.4	[0.2,1.0]
None†	39	16			

NA, Not applicable; NS, Not significant; S, Significant
* Not analyzed (too few events).
† Reference variable (see text).
‡ $P<.05$.
§ $P<.01$.

TABLE VI: MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF TUMOR METASTASIS IN 150 PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	P VALUE	RELATIVE RISK	CONFIDENCE INTERVAL [95%]
Pathology tumor margins (base involved, lateral and base involve, and clear† versus lateral margin involved)	.005*	5.7	[1.7,19.0]
Melanoma touch limbus (yes† versus no)	.03‡	3.1	[1.1,8.5]

* $P<.01$.
† Reference variable.
* $P<.05$.

liver in 3, and disseminated in 1. Of those with facial lymph node involvement, the cervical nodes were first involved in 10 patients, preauricular nodes in 5, submandibular nodes in 1, nonspecified nodes in 1 patient.

According to univariate analyses, the variables predictive of tumor metastasis included melanoma quadrant inferior ($P = .0009$) 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 2 mm or more from the limbus ($P = .03$), initial surgical technique of excisional biopsy without cryotherapy and alcohol corneal epitheliectomy ($P = .03$), and right eye ($P = .04$) (Table V). With multivariate analysis, the risk factors for metastasis included pathologic evidence of involvement of lateral tumor margin ($P = .002$) and melanoma not touching the limbus ($P = .04$) (Table VI).

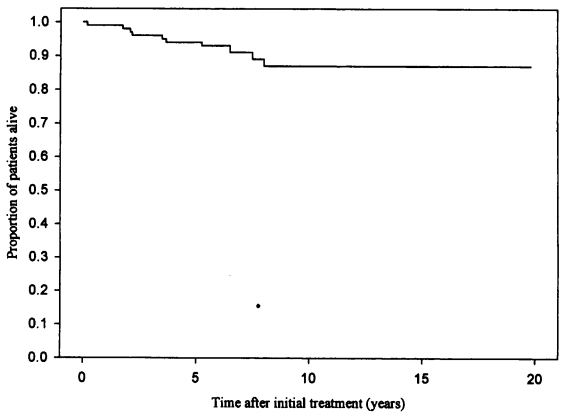

FIGURE 8.
Kaplan-Meier estimates of patients free of tumor-related death in 150 consecutive patients with surgically treated conjunctival melanoma.

Death

Of the 150 patients, 12 (8%) died from metastatic melanoma. According to Kaplan-Meier survival estimates, 7% of patients were dead by 5 years and 13% by 8 years (Fig 8).

According to univariate analyses, the factors predictive of melanoma-related death included number of local tumor recurrences 1 or more (P = .0001), signs or symptoms of lump (P = .002), melanoma in inferior quadrant (P = .01), initial tumor surgery using technique of excisional biopsy without adjuvant cryotherapy (P = .01) or cryotherapy and alcohol corneal epitheliectomy (P = .006), melanoma located in fornix (P = .02), pathologic evidence of no associated primary acquired melanosis with the melanoma (P = .02), tumor thickness 4 mm or more on gross pathologic examination (P = .02), pathologic evidence of surgical specimen with tumor at the lateral margin (P = .03) or lateral and base margins (P = .04), melanoma with greater distance from the limbus (P = .04), and tumor surgical technique prior to referral consisting of excisional biopsy without adjuvant cryotherapy (P = .04) (Table VII). According to a final multivariate analysis, the parameters linked to melanoma-related death were signs and symptoms of lump (P = .004) and pathologic evidence of no associated primary acquired melanosis with the melanoma (P = .05) (Table VIII).

DISCUSSION

In 1977, Zimmerman[22] delivered the first Algernon B. Reese Lecture, entitled "The Histogenesis of Conjunctival Melanoma." 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, Crawford[4] studied prognostic features related to metastasis of conjunctival melanoma in 19 patients. He reported these results at the annual meeting of the American Ophthalmological Society and identified the following factors related to worse prognosis: young age;

TABLE VII: UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RELATED DEATH IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO DEATH (N=138)	DEATH (N=12)	P VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Age (yr) [n=148]					
<50†	39	3			
>50	97	9	0.73	1.2	[0.4,4.6]
Sex [n=148]					
Male†	69	6			
Female	67	6	0.70	0.8	[0.2,2.7]
Eye [n=148]					
OD†	59	7			
OS	77	5	0.20	0.4	[0.1,1.4]
Signs/symptoms [n=147]					
None	3	0			
Spot†	111	4			
Lump	19	7	0.002‡	7.2	[2.1,25.0]
Irritation°	2	0			
Other°	1	0			
Prior surgery before referral [n=136]					
None	40	3	0.90	0.9	[0.2,3.7]
Incision	19	1	0.90	0.9	[0.1,7.0]
Excision†	51	6			
Excision,cryotherapy	14	0	0.04§	‖	
Excision,cryotherapy,alcohol°	2	0			

TABLE VII (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RELATED DEATH IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO DEATH (N=138)	DEATH (N=12)	P VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Prior number of recurrences before referral [n=148]			0.60	0.8	[0.5,1.5]
0	98	7			
1	29	5			
2	2	0			
≥3	7	0			
Visual acuity (initial) [n=148]			0.11	1.1	[1.0,1.3]
20/20-20/30†	112	7			
20/40-20/100	16	2	0.14	3.3	[0.7,16.2]
20/200-light perception	8	3	0.06	3.9	[1.0,16.0
Iris color [n=147]					
Blue†	41	5			
Green	15	2	0.95	0.9	[0.2,5.0]
Brown	79	5	0.35	0.6	[0.2,1.9]
Lentigo maligna eyelid [n=146]					
Yes	7	1	0.82	0.8	[0.1,6.4]
No†	127	11			
Primary acquired melanosis extension (clock hours) [n=66]					
1-3†	19	0			
4-6°	25	1			
7-9°	10	0			
10-12°	11	0			
Melanoma quadrant [n=148]					
Superior†	19	4			
Medial	25	1	0.27	0.3	[0.1,2.6]
Inferior	25	7	0.26	2.1	[0.6,7.9]
Lateral	63	0	0.01	‖	‖
Diffuse°	4	0			
Melanoma epicenter anatomic location [n=148]					
Bulbar conjunctiva†	126	10			
Fornix conjunctiva	3	1	0.02§	2.5	[1.4,107.2]
Palpebral conjunctiva	5	1	0.45	2.2	[0.3,17.5]
Plica semilunaris°	1	0			
Caruncle°	1	0			
Melanoma bulbar extension (clock hours) [n=148]			0.63	1.1	[0.8,1.4]
1-3†	106	8			
4-6	19	2	0.99	1.0	[0.2,4.7]
7-9	1	0			
10-12	1	1	0.38	2.6	[0.3,20.5]
Melanoma touch limbus [n=145]					
Yes†	85	5			
No	49	6	0.09	3.0	[0.8,10.5]
Melanoma proximity to limbus (mm) [n=145]			0.04§	1.2	[1.0,1.5]
0	83	6			
1	4	0			
2	7	1			
≥3	39	5			
Melanoma proximity to limbus (mm) [n=145]					
<2mm†	87	6			
≥2mm	46	6	0.16	2.4	[0.7,7.8]
Melanoma radial corneal involvement (mm) [n=148]			0.65	1.1	[0.8,1.4]
0	61	7			
1	17	0			
2	23	0			
≥3	35	5			

TABLE VII (CONTINUED): UNIVARIATE ANALYSIS OF THE PREDICTIVE VALUE OF CLINICAL FACTORS ON TUMOR RELATED DEATH IN A SERIES OF 150 CONSECUTIVE PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	NO DEATH (N=138)	DEATH (N=12)	*P* VALUE	RELATIVE RISK	CONFIDENCE INTERVAL (95%)
Melanoma radial corneal involvement (mm) [n=148]					
<2mm†	78	7			
≥2mm	58	5	0.76	0.8	[0.3,2.6]
Melanoma tumor base (mm) [n=141]					
<8mm†	56	3			
≥8mm	73	9	0.29	2.0	[0.6,7.5]
Melanoma tumor thickness (mm) [n=141]					
<3mm†	95	5			
≥3mm	34	7	0.05§	3.2	[1.0,10.1]
Melanoma color [n=148]					
Brown†	93	8			
Red	14	1	0.64	1.6	[0.2,13.3]
Yellow	26	3	0.60	1.4	[0.4,5.5]
Variable°	3	0			
Melanoma feeder vessel [n=147]					
Yes	52	5	0.77	1.2	[0.4,3.7]
No†	83	7			
Melanoma initial surgery after referral [n=143]					
Incision°	0	0			
Excision†	17	9			
Excision,cryotherapy	44	1	0.01§	14.5	[1.8,111.1]
Excision,cryotherapy,alcohol	64	1	0.006‡	18.3	[2.3,142.9]
Exenteration	6	1	0.90	0.83	[0.1,6.7]
Local melanoma recurrence (total number) [n=149]					
0†	92	4			
≥1	44	8	0.0001‡	15.0	[3.9,57.9]
Orbital exenteration performed [n=148]					
Yes	16	4	0.11	3.0	[0.8,11.3]
No†	120	8			
Pathology tumor thickness (gross) [n=122]			0.43	1.1	[0.9,1.4]
<1	6	2			
1	36	0			
2	33	1			
≥3	329	5			
Pathology tumor thickness (gross) [n=114]					
<4mm†	86	2			
≥4mm	22	4	0.02§	7.9	[1.4,43.1]
Pathology tumor margins (microscopic) [n=115]					
Lateral involved	9	2	0.03§	8.4	[1.2,60.4]
Base involved	11	2	0.05	7.1	[1.0,50.2]
Both lateral and base involved	3	1	0.04§	12.0	[1.1,133.4]
Margins clear†	85	2			
Pathology associated features with melanoma [n=139]					
Nevus	6	0	0.20	‖	
Primary acquired melanosis	77	2	0.02§	6.2	[1.3,28.6]
None†	44	10			

NA, Not applicable; NS, Not significant; S, Significant
° Not analyzed (too few events).
† Reference variable (see text).
‡ $P<.05$.
§ $P<.01$.
‖ No risk ratio can be calculated owing to cell with no events.

TABLE VIII: MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF DEATH IN 150 PATIENTS WITH CONJUNCTIVAL MALIGNANT MELANOMA

FACTOR	P VALUE	RELATIVE RISK	CONFIDENCE INTERVAL [95%]
Signs/symptoms (spot† versus lump)	0.004*	6.2	[1.8,21.7]
Pathology associated features with melanoma (primary acquired melanosis versus none†)	0.05	0.2	[0.04,1.0]

* $P<.01$.
† Reference variable (see text).
* $P<.05$.

tumor location in the caruncle, fornix, or palpebral conjunctiva; high mitotic activity; and lack of pathologic evidence of inflammation. At a later annual meeting of the American Ophthalmological Society, Jakobiec[23] presented 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 primary acquired melanosis in a middle-aged patient.[16,17,24,25] In this study of 150 cases, the mean tumor size was 8 mm in 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; these include presentation as a mass in the tarsus (4%), fornix (3%), plica semilunaris (1%), and caruncle (1%).[26] Lack of pigmentation within the mass, imparting a yellow or reddish pink appearance to the tumor, was found in 30% of patients, more often in those patients who had had prior excisions. Recurrent conjunctival melanoma often presents as an amelanotic mass and may be mistaken for pyogenic granuloma in a patient who has had multiple previous excisions of conjunctival melanoma.

Conjunctival melanoma is proposed to originate from preexisting conjunctival nevus, from primary acquired melanosis, or de novo.[7,27-29] Our results disclosed histopathologic evidence of possible origin from nevus in only 4%, from primary acquired melanosis in 57%, and de novo in 39%. Norregaard and associates[11] found a slightly different distribution: nevus in 16%, primary acquired melanosis in 36%, and de novo in 47%. It was somewhat surprising to find in our study that those patients with tumors arising from primary acquired melanosis 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 primary acquired melanosis, but in fact, those tumors that arose de novo carried a greater risk for exenteration and death. In the dermatologic literature, it is recognized that cutaneous melanoma that arises from lentigo maligna carries a better overall prognosis, with 10% regional metastases, compared with a metastatic rate of about 30% to 50% with nodular cutaneous melanoma.[30] Lentigo maligna is comparable to primary acquired melanosis, and the behavior of the malignant melanoma that they spawn may be similar.[31]

The association of other cutaneous diseases with conjunctival melanoma and nevi has been investigated.[32-36] Several investigators have speculated on the relationship of simultaneous or sequential conjunctival melanoma with cutaneous melanoma and cutaneous dysplastic nevus syndrome.[37] Bataille and associates[38] 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 primary acquired melanosis. 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, 7 patients had cutaneous melanoma, and 3 patients had a family history of cutaneous or uveal melanoma. The occurrence of such relatively rare tumors in the same individual by chance would be unlikely.[38] Other investigators[39,40] 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.

Recently, it has been recognized that conjunctival epithelial malignancies such as squamous papilloma and squamous cell carcinoma occur with a higher frequency in

immunosuppressed patients.[41] No patients in this study with conjunctival melanoma were immunosuppressed except for 1 patient who was taking oral corticosteroids. In addition, there were no patients who had had previous ocular radiotherapy.

Only a few studies have investigated details of the clinical features and management of conjunctival melanomas, since few clinicians have had experience with more than 1 case of this rare tumor. Lommatzsch and coworkers[8] reviewed the therapeutic outcome of 81 patients with conjunctival melanoma. Despite extensive, planned treatment with excision, cryotherapy, and radiotherapy, 24% of patients had local recurrence and 23% died from metastases at 10 years, primarily because of larger tumor size. These investigators did not analyze the effect of treatment technique or adjunctive methods such as cryotherapy or radiotherapy on patient outcome. Paridaens and coworkers,[10] in a review of 256 cases, identified unfavorable locations for conjunctival melanoma, including palpebral, forniceal, plica, caruncle, and lid margin portions of the conjunctiva. They did not assess treatment technique in their report, although they subsequently provided an exhaustive review of 95 patients in which early orbital exenteration was found not beneficial for long-term 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 and coworkers[11] studied 55 cases of conjunctival melanoma in Denmark and found that mutilating treatment (exenteration or enucleation) showed no statistical difference in patient prognosis than conservative treatment (excision with or without radiotherapy). They suggested that conservative therapy was thus reasonable when planning treatment strategy. In a previous report from our department,[12] we found that cryotherapy as a supplement to excisional biopsy was effective in preventing tumor recurrence. The goal of our present study was to more clearly define the clinical and therapeutic risks related to unfavorable outcome with conjunctival malignant melanoma.

In our study, local tumor recurrence was found in 26% at 5 years and 51% at 10 years, similar to previous reports.[11] Recurrence was related to tumor not touching the limbus and tumor extension to the margins on histopathologic examination. 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 camoflaged 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, because 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 re-excision 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.[19] In some instances, plaque radiotherapy is used.[42]

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, poor vision, probably indicates advanced or recurrent disease with multiple previous surgeries performed before referral. With repeated surgery to the conjunctiva, the tissue becomes scarred, the cornea becomes dry or astigmatic, and judgment 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 if the patient has had previous 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.[43] Extensive experience with exenteration for conjunctival melanoma has found that early rather than late exenteration has no benefit for patient survival.[9]

Overall, metastatic disease from conjunctival melanoma has been found in 14% to 27% of patients, and 10 years after diagosis, about 30% of patients have died of metastases.[3,5-7,10,11,14] Most of the studies investigating the clinical and pathologic factors related to metastasis and death from conjunctival melanoma have emanated from pathology laboratories or national cancer registries.[3-7,9-11,13] The most important factors that affect patient outcome are greater tumor thickness and base and a mixed or epithelioid cell type; if primary acquired melanosis is present along with the melanoma, then the following factors are significantly related to patient death: the presence of atypical melanocytes, pagetoid invasion, in situ growth pattern, caruncular and palpebral involvement, rarity of small polyhedral cell, lack of inflammation, and high mitotic activity.[3,6,14]

The rate of metastases in our study was 16% at 5 years and 26% at 10 years. The parameters predictive of 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.

Melanoma-related death occurred in 7% patients at 5 years and 13% at 8 years. These results are slightly more favorable than in other reports, in which the death rate was 30% to 40% at 10 years.[3,9,11] This difference may reflect a bias in patient selection, in that the pathology-based studies may find more advanced cases than this clinically based report. It may also reflect an aggressive management of metastatic melanoma with complete lymph node dissection, since most of the metastases involved the facial lymph nodes, and often adjuvant chemotherapy, radiotherapy, or immunotherapy were used. With longer follow-up, increased mortality rates may be found. However, these favorable results could also indicate that treatment by experienced ocular oncologists and medical oncologists, familiar with the disease, may improve prognosis. In previous reports, there may have been many different surgeons providing convenient care for patients outside major ocular oncology centers but submitting their specimens to the pathology laboratory, thus being included in a large series. The varied experience 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 case.

The risks for death from a univariate analysis include the type of previous 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 ocular oncology center; number of local tumor recurrences; and pathologic features of greater tumor thickness, microscopic margins involved with tumor, and lack of primary acquired melanosis with the melanoma. It is apparent that the technique of surgery is important for the patient's prognosis. The lack of supplemental cryotherapy and/or alcohol corneal epitheliectomy at excisional biopsy was related to worse prognosis. The preferred surgical approach to conjunctival malignancies is the no-touch technique of microsurgical excisional biopsy with 3 to 4 mm of tumor-free margins combined with supplemental cryotherapy to the remaining conjunctival margins and alcohol corneal epitheliectomy for corneal involvement.[19] Cryotherapy has been advocated for nearly 20 years for treatment of primary acquired melanosis as well as for supplemental treatment after excision of conjunctival melanoma.[19,44-47] Absolute alcohol corneal epitheliectomy has been used for limbal tumors or tumors with corneal involvement, as well as for scleral treatment, for over 10 years.[19] 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 from conjunctival melanoma included signs and symptoms of a lump, likely reflecting large tumor size, and lack of associated primary acquired melanosis with the melanoma on pathologic examination. Large or thicker melanoma, whether arising in the skin or conjunctiva, carries a worse prognosis. Stefani[48] found that tumors over 1.4 mm thick carry 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 predictive of death, lack of primary acquired melanosis, is more difficult to understand. The relatively favorable prognosis found with conjunctival melanoma–associated primary acquired melanosis may be related to several factors. The flat precursor pigment of primary acquired melanosis may allow for early detection of conjunctival melanoma. Other investigators have similarly found a better prognosis in patients with conjunctival melanoma arising from primary acquired melanosis, whereby the 10-year survival was 86% versus 69% for those that arose de novo.[11] However, some reports show no better prognosis in those patients with conjunctival melanoma with primary acquired melanosis.[6] Other factors may explain the more favorable prognosis of conjunctival melanoma with primary acquired melanosis, and 1 of these relates to the similarity of primary acquired melanosis to lentigo maligna. This factor is not well understood. On review of the cutaneous melanoma literature, it is evident that cutaneous melanoma arising from lentigo maligna carries a better prognosis than melanoma arising de novo.[30,49,50] Conjunctival melanoma arising in primary acquired melanosis resembles lentigo maligna melanoma arising in lentigo maligna, and both often affect the ocular region of the patient at the same time.[31,32]

Our results should be interpreted with caution. First, the patient database may be biased toward more advanced disease referred to an ocular oncology center, thus inappropriately weighting the incidence of recurrence, exenteration, metastasis, and death. Second, there is more 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 managing 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 are found on most pathology reports. Third, one cannot presume that the treatment itself had significant effect on patient longevity, since there may be yet unrecognized

factors to explain this effect. 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.

CONCLUSIONS

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. However, with astute recognition of the disease and early detection, we may be able to control the size and extent and other associated findings. Most important, however, we can control the type of surgery used.

On the basis of results of this study, the technique of surgery may affect ultimate tumor recurrence, need for orbital exenteration, tumor metastasis, and patient death. Incisional biopsy should be avoided because it increases the patient's ultimate risk of more than 1 recurrence. Excisional biopsy alone, without cryotherapy and alcohol corneal epitheliectomy, should also be avoided, if possible, since it may pose a risk for eventual orbital exenteration, metastasis, and patient death. However, until randomized studies regarding surgical technique for conjunctival melanoma are performed, the true impact of surgical manipulation cannot be determined. We advocate, if possible, that these conjunctival malignancies be managed with a no-touch technique that uses wide microsurgical excisional biopsy, cryotherapy, and alcohol epitheliectomy, as outlined in the literature.[19] This is an important factor that we, as clinicians and surgeons, can improve for our patients.

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