Published in final edited form as:

Cornea. 2018 October ; 37(10): 1287–1291. doi:10.1097/ICO.0000000000001651.

Conjunctival Squamous Neoplasia: Staging and Initial Treatment

Claudine Bellerive, MD[*,†], **Jesse L. Berry, MD**[‡], **Ashley Polski, MD**[‡], and **Arun D. Singh, MD**[*]

[*]Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH;

[†]Centre Universitaire d'ophtalmologie, CHU de Quebec, Quebec, Canada;

[‡]The USC Roski Eye Institute, Keck School of Medicine, Los Angeles, CA.

Abstract

Purpose: To evaluate the clinical relevance of the American Joint Committee on Cancer (AJCC) classification in the initial management of squamous neoplasia of the conjunctiva.

Methods: This retrospective study enrolled 95 histopathologically proven cases of treatment-naive conjunctival squamous neoplasia. Tumors were classified into 4 histological groups: conjunctival intraepithelial neoplasia (CIN) with mild dysplasia (grade 1/3), moderate dysplasia (grade 2/3), severe dysplasia (grade 3/3 or carcinoma in situ), and invasive squamous cell carcinoma (SCC). Clinical findings such as tumor location, largest basal diameter, growth pattern, and adjacent structures involved were recorded.

Results: CIN was observed in 74 cases (78%), and SCC was noted in 21 cases (22%). Based on the AJCC classification, all the 74 cases of CIN were classified as Tis (tumor in situ). Among the invasive SCC, there were 3 T1 tumors, 2 T2 tumors, and 16 T3 tumors. Complete excision with or without adjuvant therapy was selected as initial treatment in 80% of cases (76/95). Two cases of SCC with scleral invasion were treated using brachytherapy.

Conclusions: The AJCC stage does not correlate with the initial treatment of CIN. The AJCC T3 category should be reviewed to differentiate diffuse SCCs with broad surface extension from tumors with deep scleral invasion.

Keywords

conjunctiva; squamous neoplasia; AJCC staging; treatment

Depending on the histopathologic findings, conjunctival squamous neoplasia is divided into carcinoma in situ/conjunctival intraepithelial neoplasia (CIN grade 1–3), which involves the epithelium only, and invasive squamous cell carcinomas (SCC). Invasive SCC implies that neoplastic cells have broken through the basement membrane and invaded the underlying stroma.[1] The classification for conjunctival squamous neoplasia was recently reviewed by the American Joint Committee on Cancer (AJCC, eighth edition).[2] This classification system is based on 2 main primary tumor features: the degree of the depth of invasion,

Correspondence: Arun D. Singh, MD, Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Mail code: i32, 9500 Euclid Avenue, Cleveland, OH 44195 (singha@ccf.org).

The authors have no funding or conflicts of interest to disclose.

which requires histopathologic evaluation, and the size and extent of the adjoining structures involved (eg, cornea, lid, orbit), which can be determined clinically and by imaging studies.

Although the AJCC does not indicate the need for biopsy, diffuse disease that has not invaded the stroma should be classified as Tis (tumor in situ). However, the presence or absence of stromal invasion cannot be ascertained without histopathologic analysis. Further subdivisions of invasive SCC from T1 to T4 are based on the largest basal dimension (LBD) of the tumor (T1 ≤ 5 mm and T2 > 5 mm) and the presence of involvement of adjacent structures (T3 or T4) as determined by clinical examination and imaging studies (Table 1).[2] Although the T4 category includes all conjunctival tumors with orbital or further extension (bone, sinus, and brain), the T3 category encompasses a wide spectrum of tumors with broad surface extension to the cornea and eyelid and/or deep invasion of the sclera and other intraocular compartments.

Several recent retrospective case series have used the AJCC classification based on clinical presentation alone without biopsy for histopathological evaluation.[3,4] In addition, misclassification has been reported even in the presence of histopathologic confirmation.[5–8]

In this study, we evaluated the relevance of the revised AJCC classification for determining the initial management of biopsy-confirmed patients with conjunctival squamous neoplasia, with an emphasis on the wide distribution of anatomic ocular involvement encompassed by stage T3.

MATERIALS AND METHODS

We reviewed the records of 95 patients with biopsy-proven conjunctival squamous neoplasia (CIN or invasive SCC) managed at 2 medical centers: Cole Eye Institute, Cleveland Clinic, and the USC Roski Eye Institute, Keck School of Medicine, between January 2004 and December 2016. All patients with primary conjunctival squamous neoplasia who had undergone diagnostic biopsy before treatment were included. Patients who had been treated before biopsy were excluded. We obtained institutional review board approval for this retrospective study. Demographic information included age, sex, laterality, immune status, and previous treatment before referral. All patients underwent a complete slit-lamp and fundus examinations at the initial presentation. Clinical data including tumor location, LBD, growth pattern, and invasion of adjacent structures (ie, plica, caruncle, cornea, sclera, tarsal and forniceal conjunctiva, lacrimal punctum, eyelid, intraocular compartments, and orbit) were recorded. Corneal extension was measured in clock hours. Slit-lamp photographs were taken for documentation. Orbital signs and palpation of preauricular and submandibular lymph nodes were examined to evaluate for regional extension.

Diagnostic biopsy (excisional or incisional) was obtained for all patients included in this study. Excisional biopsy was performed respecting a 2-mm safety margin. In cases with corneal extension, involved corneal epithelium with 1-mm uninvolved epithelium beyond the visible tumor margin was removed after denaturation with absolute alcohol for 1 minute. In cases of suspected scleral invasion, a partial-thickness scleral flap was created in an attempt to have a tumor-free margin. The conjunctival, limbal, and corneal components of the tumor

(if applicable) were excised as a single piece and submitted in formalin for histopathology. Double freeze–thaw cryotherapy was then applied to the conjunctival margins. Depending on the size of the wound defect, the conjunctiva was either closed primarily or with a graft (amniotic membrane or autoconjunctival graft). For extensive tumors that could not be completely excised, incisional biopsy of approximately 4 mm was obtained, and the conjunctiva was left to heal by secondary intention. In cases of suspected eyelid invasion, cylindrical samples of the tarsal conjunctiva and tarsus using a 2.5-mm punch were obtained. If diagnostic biopsy was performed elsewhere, the slides were reviewed by the Cleveland Clinic Department of Pathology. We classified conjunctival squamous neoplasia into 4 groups: mild dysplasia (CIN grade 1/3), moderate dysplasia (CIN grade 2/3), severe dysplasia (CIN grade 3/3, carcinoma in situ), and invasive SCC.

RESULTS

Clinical Aspects

A total of 95 cases of treatment-naive conjunctival squamous neoplasia (CIN or invasive SCC) were included in this study. A male predominance [75 men (79%) and 20 women (21%)] was observed. Median age at diagnosis was 72 years (mean 71 years; range 45–98 years). Five patients were immunosuppressed at the time of the diagnosis. The right eye was affected in 42 patients (44%) and left eye in 53 patients (56%). Based on clinical appearance, tumors were classified as nodular in 78 cases (82%). Of these, the median LBD was 6.0 mm (mean 6.6 mm; range 2.5–18 mm). Fifteen cases were diffuse, and 2 cases were multifocal (defined by at least 2 separate lesions). The most frequent bulbar conjunctival quadrant involved was nasal (40 patients; 42%), followed by the temporal (32 patients; 34%) and inferior quadrants (2 patients; 2%). Two or more quadrants were affected in 19 cases (20%), and 2 patients presented with corneal and limbal involvement sparing the bulbar conjunctiva (Table 2).

Histopathology

Histopathologic evaluation was performed in all cases: excisional biopsy in 74 cases (78%) and incisional biopsy in 21 cases (22%). Among the 74 cases of CIN, mild dysplasia [CIN grade 1/3, 17 cases (23%)], moderate dysplasia [CIN grade 2/3, 12 cases (16%)], and severe dysplasia or carcinoma in situ [CIN grade 3/3, 45 cases (61%)] were observed. Invasive SCC was noted in 21 cases (22%) (Table 2). The limbus and cornea were involved in 59 patients with CIN (80%) and 14 patients with invasive SCC (61%). Most cases of CIN showed limbal and corneal involvement of 3 clock hours or fewer (54 patients; 73%). In cases of invasive SCC, limbal and corneal involvement was 3 clock hours or fewer in 16 patients (76%), up to 6 clocks hours in 4 patients (19%), and more than 50% in 1 patient (5%). The presence of eyelid margin/lamella invasion was noted in 3 cases of CIN, and scleral involvement was confirmed in 1 case of invasive SCC (Table 2).

AJCC Classification

Based on the AJCC classification, 74 cases were classified as Tis, 3 cases were staged T1, 2 cases were staged T2, and 16 cases were classified as T3 based on the structure involved. There was no case of SCC invading the extraocular structures (T4 category). The tumor

classification of our cohort compared with previous studies reporting the distribution of cases according to the AJCC is presented (Table 3).

Initial Management

At presentation, most patients (80%) were treated by complete excision and cryotherapy (59 Tis, 3 T1, 2 T2, and 12 T3 tumors). To reduce the risk of tumor recurrence in the case of positive surgical margins, local adjuvant therapy including interferon (IFN) α−2B (injections or drops), fluorouracil (5-FU) 1%, or mitomycin C (MMC) 0.04% was given to 8 of these patients (5 Tis and 3 T3 tumors). Two patients also underwent brachytherapy for scleral invasion. Incisional biopsy was followed by multiple sessions of cryotherapy in 1 patient and topical chemotherapy as primary treatment in 16 patients. Of them, 8 patients received topical MMC (1 mg/mL 4 times daily for 4 weeks) and 8 patients were treated with topical IFN α−2B [3 million IU/mL eye drops 4 times daily for 3–6 months (with or without intralesional injections) (Table 4)].

Subsequent Management

Over a mean follow-up duration of 19 months, recurrences occurred in 11% of cases (8/76; 6 Tis and 2 T3 tumors) treated by complete excision (with or without adjuvant therapy). Half of them had negative surgical margins on histopathology. For incisional biopsy cases followed by local adjuvant therapy for diffuse conjunctive squamous neoplasia, recurrences occurred after resolution of clinical disease in 24% (4/17; 3 Tis and 1 T3 tumors) over a mean follow-up duration of 18 months. No recurrence was observed in the 2 cases with scleral invasion treated by brachytherapy.

DISCUSSION

The accuracy of the AJCC classification as a predictive tool for the risk of tumor recurrence and metastases has been reported previously (Table 5).[3,5,7–10] However, the AJCC stage does not seem to predict the response to initial therapy. In this study, we investigated the relevance of AJCC staging of conjunctival squamous neoplasia in guiding the initial management.

Our data highlight that the majority of conjunctival carcinomas (80%) can be staged Tis tumor, which differs from previously reported retrospective case series (Table 3). This difference may be due to the inadequate use of the AJCC classification because it relates to pathological analysis instead of depending on clinical findings alone. In a study conducted by Galor et al, 389 patients of a cohort of 612 patients with conjunctival carcinomas were selected and classified into T1 to T4 categories, without any tumor staged in the Tis category.[5] In a cohort of 98 conjunctival carcinomas, Nanji et al[8] reported 0 patients with Tis; however, less than half had a biopsy-proven confirmation of SCC (suggesting that the other half were classified without biopsy). Similarly, Chauhan et al[7] showed that only 5% of cases (n = 3/64) had a histopathological diagnosis of SCC, but the authors did not classify any conjunctival carcinomas as Tis. In contrast, our study demonstrates that with appropriate biopsy, most conjunctival squamous neoplasia cases are staged as Tis. Actually, the tumor

distribution in our series closely resembles that of the only other published study, in which all cases were biopsy-proven similar to the series of the present study.[10]

Recent advances in the field of medical management (immunotherapy and chemotherapy) of conjunctival carcinomas are promising. Excellent outcomes have been reported with topical IFN α 2-B as primary treatment for diffuse conjunctival and/or corneal disease, and as a postoperative adjuvant therapy in cases of positive margins or recurrence.[8,11–16] Furthermore, IFN α 2-B is reported to be equally effective as topical chemotherapeutic agents including MMC and 5-FU in achieving tumor regression and is associated with a lower rate of complications regardless of the dosing regimen used.[17–19] However, the initial treatment of T3 tumors (diffuse tumors) with corneal extension (and sparing the sclera) was the same as the treatment of Tis tumors involving the cornea, and both topical IFN and complete excision were successfully used as treatment modalities.

In our cohort, there were only 2 cases of SCC invading the sclera, both of which were treated by brachytherapy (T3 deep invading tumors). The authors do not recommend topical medical therapies for scleral invasion. Because of its limited ocular penetration, it is well established that topical or intralesional IFN is unsuccessful and thus not indicated in treatment of invasive SCC into the sclera. As an alternative to enucleation or orbital exenteration, we performed surface brachytherapy.[20] Arepalli et al[21] reported 15 cases of SCC biopsy-proven for scleral invasion managed by brachytherapy. Except for 4 patients who experienced distant conjunctival recurrence, local tumor control was achieved in all cases at a mean follow-up of 42 months. A retrospective study including 8 cases of recalcitrant SCC pathologically confirmed showed similar outcomes with electron beam radiation.[22]

In conclusion, this study provides a realistic picture of the conjunctival squamous neoplasia distribution based on the AJCC criteria using the histopathologic and anatomic definitions. AJCC staging of conjunctival squamous neoplasia does not seem to be a reliable guide for initial management because both surgery and topical medications were used for Tis to T3 tumors. Our study further suggests that reclassification of the T3 category (diffuse vs. deep invading) is indicated to better guide initial treatment for patients.

REFERENCES

1. Margo CE, White AA. Ocular surface squamous neoplasia: terminology that is conceptually friendly but clinically perilous. Eye. 2014;28:507–509. [PubMed: 24807632]
2. Conway RM, Graue GF, Pelayes DE, et al. Conjunctival Carcinoma. American Joint Committee on Cancer (AJCC) AJCC Cancer Staging Manual 8th ed. New York, NY: Springer; 2017.
3. Shields CL, Kaliki S, Kim HJ, et al. Interferon for ocular surface squamous neoplasia in 81 cases: outcomes based on the American Joint Committee on Cancer classification. Cornea. 2013;32:248–256. [PubMed: 22580436]
4. Shah SU, Kaliki S, Kim J, et al. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: outcomes based on American Joint Committee on Cancer Classification. Arch Ophthalmol. 2012;130:159–164. [PubMed: 22332208]
5. Galor A, Karp CL, Oellers P, et al. Predictors of ocular surface squamous neoplasia recurrence after excisional surgery. Ophthalmology. 2012;119: 1974–1981. [PubMed: 22704832]

6. Kao AA, Galor A, Karp CL, et al. Clinicopathologic correlation of ocular surface squamous neoplasms at Bascom Palmer Eye Institute: 2001 to 2010. Ophthalmology. 2012;119:1773–1776. [PubMed: 22771047]
7. Chauhan S, Sen S, Sharma A, et al. American Joint Committee on Cancer Staging and Clinicopathological High-Risk Predictors of Ocular Surface Squamous Neoplasia. Arch Pathol Lab Med. 2014;138:1488–1494. [PubMed: 25357110]
8. Nanji AA, Moon CS, Galor A, et al. Surgical versus medical treatment of ocular surface squamous neoplasia: a comparison of recurrences and complications. Ophthalmology. 2014;121:994–1000. [PubMed: 24411578]
9. Parrozzani R, Frizziero L, Trainiti S, et al. Topical 1% 5-fluoruracil as a sole treatment of corneoconjunctival ocular surface squamous neoplasia: long-term study. Br J Ophthalmol. 2017;101:1094–1099. [PubMed: 27941046]
10. Yousef YA, Finger PT. Squamous carcinoma and dysplasia of the conjunctiva and cornea. Ophthalmology. 2012;119:233–240. [PubMed: 22189448]
11. Zarei-Ghanavati S, Alizadeh R, Deng SX. Topical interferon alpha-2b for treatment of noninvasive ocular surface squamous neoplasia with 360 degrees limbal involvement. J Ophthalmic Vis Res 2014;9:423–426. [PubMed: 25709765]
12. Sturges A, Butt AL, Lai JE, et al. Topical interferon or surgical excision for the management of primary ocular surface squamous neoplasia. Ophthalmology. 2008;115:1297–1302. [PubMed: 18294690]
13. Kim HJ, Shields CL, Shah SU, et al. Giant ocular surface squamous neoplasia neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. Ophthalmology. 2012;119:938–944. [PubMed: 22361315]
14. Schechter BA, Koreishi AF, Karp CL, et al. Long-term follow-up of conjunctival and corneal intraepithelial neoplasia treated with topical interferon alfa-2b. Ophthalmology. 2008;115:1291–1296. [PubMed: 18187195]
15. Karp CL, Moore JK, Rosa RH, Jr. Treatment of conjunctival and corneal intraepithelial neoplasia with topical interferon alpha-2b. Ophthalmology. 2001;108:1093–1098. [PubMed: 11382635]
16. Boehm MD, Huang AJ. Treatment of recurrent corneal and conjunctival intraepithelial neoplasia with topical interferon alfa 2b. Ophthalmology. 2004;111:1755–1761. [PubMed: 15350333]
17. Poothullil AM, Colby KA. Topical medical therapies for ocular surface tumors. Semin Ophthalmol. 2006;21:161–169. [PubMed: 16912014]
18. Galor A, Karp CL, Chhabra S, et al. Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: a dose comparison study. Br J Ophthalmol. 2010;94:551–554. [PubMed: 19493859]
19. Huerva V, Mangues I. Treatment of conjunctival squamous neoplasias with interferon alpha 2b. J Fr Ophtalmol. 2008;31:317–325. [PubMed: 18404128]
20. Aronow ME, Singh AD. Radiation therapy: conjunctival and eyelid tumors. Dev Ophthalmol. 2013;52:85–93. [PubMed: 23989129]
21. Arepalli S, Kaliki S, Shields CL, et al. Plaque radiotherapy in the management of scleral-invasive conjunctival squamous cell carcinoma. JAMA Ophthalmol. 2014;132:691–696. [PubMed: 24557333]
22. Graue GF, Tena LB, Finger PT. Electron beam radiation for conjunctival squamous carcinoma. Ophthal Plast Reconstr Surg. 2011;27: 277–281.

TABLE 1.

Definition of Primary Tumor (T).[2]

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor (≤5 mm in the greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures
T2	Tumor (>5 mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures
T3	Tumor invades adjacent structures (excluding the orbit)
T4	Tumor invades the orbit with or without further extension
T4a	Tumor invades orbital soft tissue without bone invasion
T4b	Tumor invades the bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades the brain

TABLE 2.

Conjunctival Squamous Neoplasia: Clinical and Pathologic Features

Characteristics	Total, n = 95 (%)	Patients with CIN, n = 74 (%)	Patients with SCC, n = 21 (%)
Age (yr)			
≤70	44 (46)	36 (49)	8 (38)
>70	51 (54)	38 (51)	13 (62)
Sex			
Male	75 (79)	59 (80)	16 (76)
Female	20 (21)	15 (20)	5 (24)
Laterality			
OD	42 (44)	29 (39)	13 (62)
OS	53 (56)	45 (61)	8 (38)
Growth pattern			
Nodular	78 (82)	60 (81)	18 (86)
Diffuse	15 (16)	12 (16)	3 (14)
Multifocal	2 (2)	2 (3)	0 (0)
Tumor location			
Cornea/limbus	73 (77)	59 (80)	14 (67)
Bulbar conjunctiva	93 (98)	72 (97)	21 (100)
Tarsal conjunctiva	7 (7)	6 (8)	1 (5)
Fornix	8 (8)	7 (9)	1 (5)
Caruncle	7 (7)	4 (5)	3 (14)
Eyelid margin/lamella	4 (4)	3 (4)	1 (5)
Sclera	2 (2)	0 (0)	2 (10)
Biopsy			
Incisional	21 (22)	17 (23)	4 (19)
Excisional	74 (78)	57 (77)	17 (81)
Histopathologic grade			
Mid dysplasia (1/3)	—	17 (23)	—
Moderate dysplasia (2/3)	—	12 (16)	—
Severe dysplasia (3/3)	—	45 (61)	—
AJCC stage			
Tis	74 (78)	74 (100)	—
T1	3 (3)	—	3 (14)
T2	2 (2)	—	2 (10)
T3	16 (17)	—	16 (76)

TABLE 3.

Conjunctival Squamous Neoplasia: Distribution According to the AJCC Stage

AJCC Stage	Chauhan, 2014[7] (N = 64)	Nanji, 2014[8] (N = 98)	Shields, 2013[3] (N = 81)	Yousef, 2012[10] (N = 101)	Shah, 2012[4] (N = 23)	Galor, 2012[5] (N = 381)	This Study
Tis	0 (0%)	0 (0%)	10 (12%)	59 (58%)	3 (13%)	0 (0%)	74 (78%)
T1	4 (6%)	18 (18%)	13 (16%)	7 (7%)	0 (0%)	201 (53%)	3 (3%)
T2	39 (61%)	10 (10%)	6 (7%)	1 (1%)	0 (0%)	140 (37%)	2 (2%)
T3	4 (6%)	70 (72%)	51 (63%)	32 (32%)	20 (87%)	36 (9%)	16 (17%)
T4	17 (27%)	0 (0%)	1 (1%)	2 (2%)	0 (0%)	4 (1%)	0 (0%)

TABLE 4.

Conjunctival Squamous Neoplasia: AJCC Stage and Initial Management

Management	Tis (N)	T1 (N)	T2 (N)	T3 (N)	Total (N)
Complete excision	54	3	2	8	67
Complete excision combined with IFN or MMC *	5	0	0	4	9
Topical MMC	8	0	0	0	8
IFN (injections ± topical)	6	0	0	2	8
Cryotherapy	1	0	0	0	1
Brachytherapy †	0	0	0	2	2
Total (N)	74	3	2	16	95

* All cases who received adjuvant therapy to excision had positive margins.

† All 2 cases treated by brachytherapy had scleral invasion.

TABLE 5.

Conjunctival Squamous Neoplasia: AJCC Stage and Response to Treatment, Recurrence, and Metastasis

Author/Year	Response to Treatment	Local Recurrence	Metastasis
Parrozzani, 2017[9]	Topical 5-FU T1 versus T2 or T3 Not predictive		
Shields, 2013[3]	IFN only versus IFN + surgery Not predictive		
Chauhan, 2014[7]		T1 or T2 versus T3 or T4 Higher risk of recurrence	T1 or T2 versus T3 or T4 Higher risk of metastases
Nanji, 2014[8]		Not predictive	
Yousef, 2012[10]		Tis versus T1 or T2 versus T3 versus T4 Higher risk of recurrence	
Galor, 2012[5]		T1 versus T3 and T2 versus T3 Higher risk of recurrence	