The Diagnostic Value of Exfoliative Cytology vs Histopathology for Ocular Surface Squamous Neoplasia

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• PURPOSE: **To determine the reliability and role of conjunctival exfoliative cytologic and histopathologic diagnosis of biopsied tissue in ocular surface squamous neoplasia.**

• DESIGN: **Retrospective review of an interventional case series of patients biopsied and treated for squamous conjunctival and corneal neoplasia.**

• METHODS: **Forty-nine patients who underwent conjunctival cytologic analysis (n = 36), conjunctival biopsy (n = 35), or both were evaluated. For the purposes of this study, three ocular pathologists reviewed the results of cytologic and biopsied tissue in a masked fashion.**

• RESULTS: **Evaluation of cytologic smears revealed a 91% concordance in interpretation of conjunctival cytologic material as no dysplasia vs dysplasia. The concordance dropped to 59% in grading the degree of dysplasia. The cytologic material was found to be inadequate for interpretation in 1 case. Evaluation of subsequent biopsy revealed a 98% concordance between the pathologists in interpretation of biopsied tissue as no dysplasia vs any degree of dysplasia. The concordance decreased to 83% in grading the degree of dysplasia. Cytologic evaluation was capable of distinguishing a neoplastic from nonneoplastic process before tissue biopsy in 80% of cases.**

• CONCLUSIONS: **Ocular surface cytologic analysis is a simple, safe, and relatively noninvasive diagnostic tool. It was found helpful in detecting dysplasia before surgical resection. It was used in the settings of recurrent tumor and for follow-up care of patients treated with topical chemotherapy. Although cytologic smears cannot replace incisional or excisional biopsy for definitive diagnosis, exfoliative cytologic analysis can play an important role in the diagnosis and management of patients with ocular surface squamous neoplasia. (Am J Ophthalmol 2009; 148:772–778. © 2009 by Elsevier Inc. All rights reserved.)**

OCULAR SURFACE SQUAMOUS NEOPLASIA (OSSN) is the most common conjunctival tumor in adults, varying in prevalence from 0.02 to 3.5 per 100,000 per year.[1–4] The term *ocular surface squamous neoplasia* encompasses the diagnoses of conjunctival intraepithelial neoplasia (CIN), carcinoma in situ, and invasive squamous cell carcinoma (SCC). Clinically, OSSN most commonly arises in the interpalpebral limbal conjunctiva. The growth may be nodular, superficial, or diffusely invasive.[4] These tumors may present as localized slowly growing lesions that mimic benign conjunctival degenerations and may coexist with pingueculae and pterygia. Rarely, diffuse tumors in older patients may be misdiagnosed as chronic unilateral conjunctivitis. Invasive squamous carcinoma directly can invade the eyelid, eye, orbit, adjacent paranasal sinus structures, and brain.[5–7] However, systemic metastases resulting from SCC are rare.

Early diagnosis and treatment decreases the risk of locally aggressive disease and can improve the patients prognosis for local control and preservation of vision.[8] Recurrence rates generally are higher for more severe grades of OSSN and have been related to the adequacy of surgical margins at initial excision.[9]

In clinical practice, squamous conjunctival and corneal tumors typically are evaluated by pathologic analysis (through cytologic or histopathologic evaluation of tissue).[10–13] In particular, we have found cytologic evaluation to be useful for the diagnosis of OSSN in the setting of recurrent tumors considered for topical chemotherapy.[14–16] However, like clinical evaluation, superficial cytologic analysis cannot differentiate between CIN, carcinoma in situ, and invasive SCC. This distinction can only be made through histopathologic evaluation of biopsied tissue. Further, interpretation of both cytologic and biopsied tissue is dependent both on the adequacy of the specimen and on the experience of the pathologist.

This study's primary goal was to determine concordance between the cytologic and histopathologic diagnoses of suspected OSSN. The secondary goals were: 1) to determine concordance between pathologists in interpreting conjunctival cytologic material and 2) to determine concordance between pathologists in interpreting conjunctival biopsies performed for suspected OSSN. The ability to obtain an accurate diagnosis affects both the treatment options for conjunctival epithelial malignancies and patient outcomes.[16–21] This study examined the concordance between cytologic and histopathologic analysis of the conjuctival biopsies as well as the concordance between the opinions of three ophthalmic pathologists (T.M., C.E.I., S.A.M.) in a tertiary ophthalmic referral center.

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TABLE 1. Carcinoma of the Conjunctiva Staging System (American Joint Committee on Cancer, 7th Edition)[a]

Tumor (T) size	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 5 mm or less in greatest dimension[b]
T2	Tumor more than 5 mm in greatest dimension, without invasion of adjacent structures[c]
T3	Tumor invades adjacent structures[c] (excluding the orbit)
T4	Tumor invades the orbit with or without further extension:
	T4a: tumor invades orbital soft tissues, without bone invasion
	T4b: tumor invades bone
	T4c: tumor invades adjacent paranasal sinuses
	T4d: tumor invades brain
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Histopathologic type	
• The classification applies only to carcinoma of the conjunctiva	
• CIN including in situ squamous cell carcinoma	
• Squamous cell carcinoma	
• Mucoepidermoid carcinoma	
• Spindle cell carcinoma	
• Sebaceous gland carcinoma including pagetoid (conjunctival) spread	
• Basal cell carcinoma	
Histologic grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated
Biomarker:	
Ki-67 growth fraction:	
• Is the Ki-67 growth fraction less than 5%?	
• Is the Ki-67 growth fraction between 5% and less than 10%?	
• Is the Ki-67 growth fraction between 10% and less than 20%?	
• Is the Ki-67 growth fraction between 20% and 50%?	
• Is the Ki-67 growth fraction >50%?	

CIN = conjunctival intraepithelial neoplasia.

[a]Reprinted with permission from Carcinoma of the conjunctiva. In: Edge SB, Byrd DR, Carducci MA, Compton CC, editors. AJCC Cancer Staging Manual. 7th ed. New York, New York: Springer (in press).

[b]Tumors occur most commonly in the bulbar limbal conjunctiva.

[c]Adjacent structures include: the cornea (3, 6, 9, or 12 clock hours), intraocular compartments, forniceal conjunctiva (lower and/or upper), palpebral conjunctiva (lower and/or upper), tarsal conjunctiva (lower and/or upper), lacrimal punctum and canaliculi (lower and/or upper), plica, caruncle, posterior eyelid lamella, anterior eyelid lamella and/or eyelid margin (lower and/or upper).

METHODS

MEDICAL RECORDS OF THE NEW YORK CANCER CENTER were searched for all consecutive patients with clinically suspected OSSN between January 2002 and February 2009. Consecutive cases with available cytologic or histopathologic material, or both, were selected for further review. Informed consent for all procedures was obtained