Recent Changes of Classification for Squamous Intraepithelial Lesions of the Head and Neck

Kyung-Ja Cho, MD, PhD; Joon Seon Song, MD, PhD

• ***Context.***—**Interpretation of atypical squamous lesions of the head and neck has always been a nettlesome task for pathologists. Moreover, many different grading systems for squamous intraepithelial lesions have been proposed in past decades. The recent World Health Organization 2017 classification presents 2 types of 2-tier systems for laryngeal and oral precursor lesions.**

Objective.—**To review the recent changes in classification and the clinical significance for squamous intraepithelial lesions of the head and neck.**

Data Sources.—**Personal experience and data from the literature.**

Conclusions.—**The 2-tier grading system for laryngeal dysplasia, presented by World Health Organization in 2017, is expected to improve diagnostic reproducibility and clinical implication. However, the diagnostic criteria for low-grade dysplasia do not distinguish it clearly from basal cell hyperplasia. The World Health Organization 2017 classification of oral epithelial dysplasia remains unclear, and complicated and variable grading systems still make head and neck intraepithelial lesions difficult to interpret.**

(*Arch Pathol Lab Med.* 2018;142:829–832; doi: 10.5858/arpa.2017-0438-RA)

Squamous cell carcinomas of the head and neck are traditionally considered to arise via sequential genetic and cytologic changes after long-term exposure to carcinogens, such as tobacco.[1] Invasive carcinomas are believed to develop from precursor lesions, but malignant potential or morphologic characteristics of precursor lesions are not yet clearly understood. The recently demonstrated association between human papillomavirus and oropharyngeal carcinoma has led this carcinoma to be categorized as a separate pathogenetic entity. Although early oropharyngeal cancer is a rare occurrence because of the deep location of those tumors, early lesions of the larynx or oral cavity are more easily detected. Those early lesions can be biopsied and submitted for interpretation to pathologists. Pathologists are required to recognize precursor lesions based on morphology or genetic analysis and to speculate on the premalignant potential of such lesions. However, there has been great variability in the naming of these lesions and in determining their clinical significance. Furthermore, the grading system proposed by oral pathologists has not simplified the diagnosis. The recent changes in the classification of squamous intraepithelial lesions of the head and neck, mainly those of the larynx and oral cavity, are discussed in this review, along with an introduction to reported clinical data.

Accepted for publication December 1, 2017.

Published as an Early Online Release May 18, 2018.

From the Department of Pathology, University of Ulsan College Medicine, Asan Medical Center, Seoul, Korea.

The authors have no relevant financial interest in the products or companies described in this article.

Presented at the 16th Spring Seminar of the Korean Pathologists Association of North America (KOPANA); March 2–4, 2017; San Antonio, Texas.

Corresponding author: Kyung-Ja Cho, MD, PhD, Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea (email: kjc@amc.seoul.kr).

LARYNGEAL DYSPLASIA

The World Health Organization (WHO) 2017 classification formally reused the term *dysplasia*,[2] rather than the previously proposed terms *squamous intraepithelial neoplasia* (SIN),[3,4] *squamous intraepithelial lesion* (SIL),[5] or *laryngeal intraepithelial neoplasia*.[6] According to the newly listed criteria, laryngeal dysplasia is classified as low grade if the basal/parabasal cell layer is unchanged or is augmented in the lower half of the epithelium, with preserved stratification and, at most, minimal cellular atypia. These criteria are partly based on the amended Ljubljana classification,[5] and ambiguity persists in distinguishing low-grade dysplasia from basal/parabasal cell hyperplasia. High-grade dysplasia is defined as showing conspicuous cellular atypia from one-half to the entire epithelial thickness.

Simplification Into a 2-Tier System

The main change between the 2017 and 2005 WHO classifications is the simplification into a 2-tier system from a 4-tier system by the unification into *high-grade dysplasia* of former *moderate dysplasia*, *severe dysplasia*, and *carcinoma in situ* (CIS),[2,7] although the category of CIS from the amended Ljubljana classification was left as a footnote. The rationale for this change came from 3 sources.

Laryngeal and Uterine Cervical Dysplasia Differ Histologically.—First, laryngeal dysplasia is histologically different from uterine cervical dysplasia, in the presence of epithelial thickening, surface maturation/keratinization, and dyskeratosis, so the classic CIS with full epithelial replacement is rare in the larynx, except for erythroplakic types. This phenomenon was described by Crissman in 1983,[8]

Crissman et al in 1988,[9] and Crissman and Zarbo in 1989.[10] The study in 1989 demonstrated that severe keratinizing dysplasia had a greater frequency of progression to squamous cell carcinoma than full-thickness CIS had and recommended combining the 2 lesions into SIN grade III.[10] The same group further modified the 3-tier system into a 2-tier system, namely SIN I (low grade) and SIN II (high grade), as published in book chapters.[3,4]

High Levels of Interobserver Variability.—Second, interobserver variability of the previous 4- or 3-tier classifications proved high in many studies, with concordance rates of 13% to 60%.[11–14] When 3 pathologists compared various combinations of WHO, SIN, and SIL classifications for 110 laryngeal premalignant lesions, the concordance rates were similar among the 3 systems but were greater when 4 or 3 categories were grouped into 3 or 2 categories.[11] Thus, the WHO 2017 classification is expected to provide better reproducibility.

Clinical Differences Were Difficult to Identify.—Third, the clinical difference between CIS and moderate/severe dysplasia has not been well identified. Progression rates of laryngeal dysplasia into invasive carcinoma have been reported to range from 2% to 74%, and a meta-analysis of 940 cases from 9 studies reported a pooled rate of 13.6%.[15] When histologic grades were combined into 2 groups, the malignant transformation rate was higher in the severe dysplasia–CIS group (30.4%) than in the mild to moderate dysplasia group (10.6%). Differences between the moderate and severe dysplasia groups or between severe dysplasia and CIS groups were not emphasized. Another study with a 15-year follow-up of 45 patients demonstrated greater high-progression rates, which were greater in the severe dysplasia–CIS group (53%) than they were in the mild to moderate dysplasia group (33%).[16] Two recent studies[12,17] showed remarkably similar progression rates of 8.4% in 237 and 107 cases. In both studies, the subjects included mild, moderate, and severe dysplasia and CIS, and the progression rates of the severe dysplasia and CIS groups were not different. Finally, a study with a 10-year follow-up of 86 patients showed progression rates of 40%, 20%, 15%, and 0% in the CIS, moderate dysplasia, severe dysplasia, and mild dysplasia groups, respectively.[18] It is noticeable that a higher progression rate was observed in the moderate dysplasia group than in the severe dysplasia group. All these studies are valuable, however, considering the high interobserver variability of the 4-tier system and the diverse treatments of the initial lesions, a true natural history of laryngeal dysplasias may remain difficult to understand.

Classification of laryngeal dysplasia returned to SIN I (low-grade dysplasia) and SIN II (high-grade dysplasia), as described by Crissman and Sakr.[4] Their separation criteria were slightly different from the current WHO criteria, requiring at least minor nuclear pleomorphism for low-grade dysplasia. The WHO 2017 criteria are influenced by the amended Ljubljana classification, in which no cellular atypia was required for low-grade SIL. Thus, it seems fair that a significantly lower progression rate was observed in the low-grade SIL group (1.6%) than seen in the high-grade SIL group (12.5%).[5] A diagnosis of low-grade dysplasia would be more reproducible if differential points between basal/parabasal cell hyperplasia and low-grade dysplasia were stated more clearly. The criteria for low-grade dysplasia by Crissman and Sakr[4] appear to be practical and effective (Figure 1, A and B).

ORAL EPITHELIAL DYSPLASIA

The term *oral epithelial dysplasia* (OED), which has been used since the 1980s in oral pathology, was added to the WHO 2017 classification. The grading for OED or oral precancerous lesions has been one of the most chaotic and desultory fields in pathology. Regrettably, the WHO 2017 classification of OED remains unclear, similar to the 2005 version. The list of diagnostic criteria has been modified to 8 architectural and 8 cytologic criteria from the 2005 version of 7 architectural and 9 cytologic criteria.[2,7] The reason for the modification is not stated, and the footnote that states "According to Nankivell P et al,[19] a cut-off point of four architectural and four cytological changes may improve prognostication"[2(p113)] is incorrect. The study by Nankivell et al[19] used 4 or more architectural and 5 or more cytologic features among the 2005 criteria. Moreover, the text in the 2017 WHO chapter states that "there is no good evidence to indicate how the presence of individual features could be translated into a grade of dysplasia and that dysplasia grading is poorly reproducible between observers."[2(p112)] The authors of the chapter appear not to have reached a consensus, and the content in its entirety does not help pathologists.

Complexity of Grading System Is Continued.—This grading system, by selection of histologic features among many examples, originated from the Pinborg et al[20] system, which required weighted scoring of 13 microscopic features. The dysplasia grade was classified as *mild*, *moderate*, or *severe* according to the sum of scores. The subjectivity and variability of such a method have been notorious.[21,22] Brothwell et al[23] suggested a 4-tier system according to the thickness of the increasing number of cells that showed hyperchromatism and pleomorphism. The WHO 2005 classification of oral epithelial precursor lesions contained a list of diagnostic criteria for 7 architectural and 9 cytologic categories and a 4-tier system according to the thickness involved, along with the SIN and SIL systems.[7] Kujan et al[24] proposed a binary system of *low-risk* and *high-risk* groupings according to the presence of 4 or more architectural and 5 or more cytologic features among 16 criteria. That system was evaluated to have less variability compared with the 4-tiered WHO classification.[19,24,25] The Working Group at a workshop coordinated by the WHO Collaborating Centre for Oral Cancer also recommended a 2-tier classification, using 16 criteria.[26] However, assessment of 16 histologic features in every oral biopsy case may be counterproductive in pathology practices. Other comparative studies resulted in greater interobserver agreement than those using the WHO or Brothwell classification.[7,23,27–29]

Clinical Significance of OED Is Uncertain.—When even the diagnostic criteria are unsettled, speculating on the clinical behavior of oral dysplasias might be pointless. A recent meta-analysis[30] reported that the overall malignant transformation rate for 11 423 cases of oral "leukoplakia" was 3.5%, with a range between 0.13% and 34%. One retrospective review[31] of 1248 cases of oral squamous cell carcinoma identified 25 cases (2%) with preceding dysplastic lesions. The true malignant potential of OED, either low-grade or high-grade, seems questionable at this time.

Are Laryngeal Dysplasia and OED Histologically Distinguishable?—We remain unconvinced that oral dysplasia should be evaluated by special standards that are different from those of the larynx. Histologic features of intraepithelial lesions are similar between the oral cavity and the larynx, which share epithelial thickening and keratini-

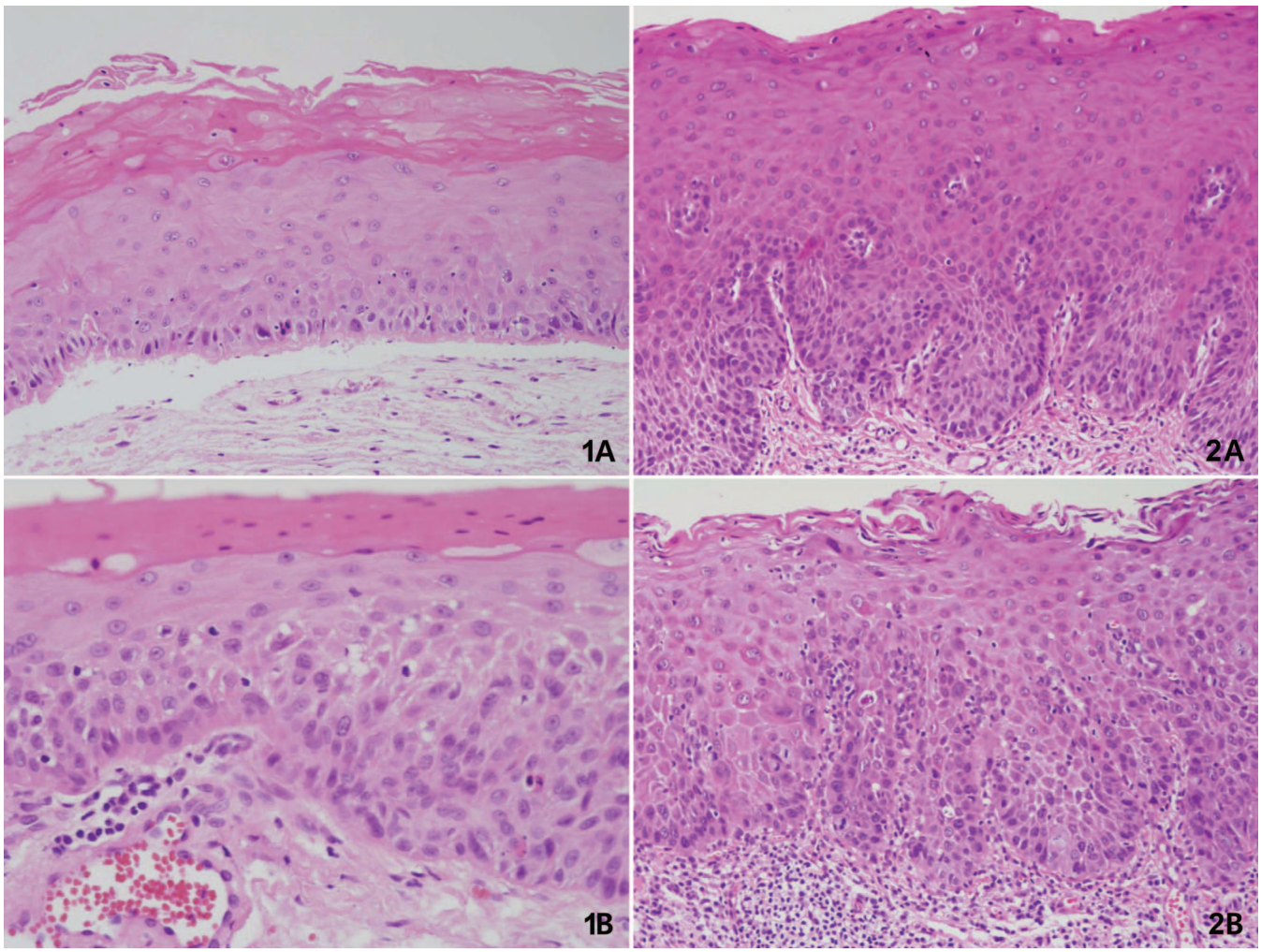

Figure 1. *A, Low-grade dysplasia of the larynx showing mild cellular pleomorphism of the basal layer. B, High-grade dysplasia showing involvement of more than the lower half of the epithelium by enlarged, atypical cells with a loss of polarity (hematoxylin-eosin, original magnification ×200 [A and B]).*

Figure 2. *A, Low-grade dysplasia of the oral cavity showing increased basal/parabasal cells with mild cellular atypia. B, High-grade dysplasia showing the upward growth of atypical cells with occasional dyskeratosis (hematoxylin-eosin, original magnification ×200 [A and B]).*

zation. Some oral intraepithelial lesions do tend to show more-noticeable rete ridge elongations than laryngeal lesions show. That feature must have been involved in the inclusion of the "drop-shaped rete ridges" criterion as one of the architectural criteria of OED. However, that difference alone does not rationalize using 16 criteria for OEDs. Application of the common 2-tier classification to oral, laryngeal, and other squamous intraepithelial lesions of the head and neck appears commendable for consistent evaluation of head and neck intraepithelial lesions (Figure 2, A and B).

SUMMARY

In summary, the 2-tier grading system for laryngeal dysplasia, presented by WHO 2017, is expected to improve diagnostic reproducibility and an understanding of clinical implications. However, the diagnostic criteria for low-grade dysplasia do not clearly distinguish it from basal cell hyperplasia. The WHO 2017 classification for oral epithelial dysplasia remains unclear and complicated, and the variable grading systems still make head and neck intraepithelial lesions difficult to interpret.

References

1. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res*. 2003;63(8):1727–1730.

2. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC Press; 2017. *World Health Organization Classification of Tumours*; vol 9.

3. Sakr WA, Gale N, Gnepp DR, Crissman JD. Squamous intraepithelial neoplasia of the upper aerodigestive tract. In: Gnepp DR, ed. *Diagnostic Surgical Pathology of the Head and Neck*. 2nd ed. Philadelphia, PA: Saunders/Elsevier; 2009;1–44.

4. Crissman JD, Sakr WA. Squamous neoplasia of the upper aerodigestive tract: Intraepithelial and invasive squamous cell carcinoma. In: Pilch BZ, ed. *Head and Neck Surgical Pathology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001;34–52.

5. Gale N, Blagus R, El-Mofty SK, et al. Evaluation of a new grading system for laryngeal squamous intraepithelial lesions—a proposed unified classification. *Histopathology*. 2014;65(4):456–464.

6. Resta L, Colucci GA, Troia M, Russo S, Vacca E, Pesce Delfino V. Laryngeal intraepithelial neoplasia (LIN): an analytical morphometric approach. *Pathol Res Pract*. 1992;188(4–5):517–523.

7. Barnes L, Eveson JW, Reichert PA, Sidransky D, eds, et al. *Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press; 2005. *World Health Organization Classification of Tumours*; vol 9.

8. Crissman JD. Laryngeal keratosis preceding laryngeal carcinoma: a report of four cases. *Arch Otolaryngol*. 1982;108(7):445–448.
9. Crissman JD, Zarbo RJ, Drozdowicz S, Jacobs J, Ahmad K, Weaver A. Carcinoma in situ and microinvasive squamous carcinoma of the laryngeal glottis. *Arch Otolaryngol Head Neck Surg*. 1988;114(3):299–307.
10. Crissman JD, Zarbo RJ. Dysplasia, in situ carcinoma, and progression to invasive squamous cell carcinoma of the upper aerodigestive tract. *Am J Surg Pathol*. 1989;13(suppl 1):5–16.
11. Fleskens SA, Bergshoeff VE, Voogd AC, et al. Interobserver variability of laryngeal mucosal premalignant lesions: a histopathological evaluation. *Mod Pathol*. 2011;24(7):892–898.
12. Hu Y, Liu H. Diagnostic variability of laryngeal premalignant lesions: histological evaluation and carcinoma transformation. *Otolaryngol Head Neck Surg*. 2014;150(3):401–406.
13. Sarioglu S, Cakalagaoglu F, Elagoz S, et al. Inter-observer agreement in laryngeal pre-neoplastic lesions [published correction appears in *Head Neck Pathol*. 2010;4(4):281]. *Head Neck Pathol*. 2010;4(4):276–280.
14. Fleskens S, Slootweg P. Grading systems in head and neck dysplasia: their prognostic value, weaknesses and utility. *Head Neck Oncol*. 2009;1:11.
15. Weller MD, Nankivell PC, McConkey C, Paleri V, Mehanna HM. The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case series and meta-analysis. *Clin Otolaryngol*. 2010;35(5):364–372.
16. Spielmann PM, Palmer T, McClymont L. 15-Year review of laryngeal and oral dysplasias and progression to invasive carcinoma. *Eur Arch Otorhinolaryngol*. 2010;267(3):423–427.
17. Karatayli-Ozgursoy S, Pacheco-Lopez P, Hillel AT, Best SR, Bishop JA, Akst LM. Laryngeal dysplasia, demographics, and treatment: a single-institution, 20-year review. *JAMA Otolaryngol Head Neck Surg*. 2015;141(4):313–318.
18. Zhang HK, Liu HG. Is severe dysplasia the same lesion as carcinoma in situ? 10-Year follow-up of laryngeal precancerous lesions. *Acta Otolaryngol*. 2012; 132(3):325–328.
19. Nankivell P, Williams H, Matthews P, et al. The binary oral dysplasia grading system: validity testing and suggested improvement. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115(1):87–94.
20. Pindborg JJ, Reichart PA, Smith CJ, van der Waal I. *Histological Typing of Cancer and Precancer of the Oral Mucosa*. 2nd ed. Berlin, Germany: Springer; 1997.
21. Warnakulasuriya S. Histological grading of oral epithelial dysplasia: revisited. *J Pathol*. 2001;194(3):294–297.
22. Kujan O, Khattab A, Oliver RJ, Roberts SA, Thakker N, Sloan P. Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: an attempt to understand the sources of variation. *Oral Oncol*. 2007; 43(3):224–231.
23. Brothwell DJ, Lewis DW, Bradley G, et al. Observer agreement in the grading of oral epithelial dysplasia. *Community Dent Oral Epidemiol*. 2003;31(4): 300–305.
24. Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. *Oral Oncol*. 2006;42(10):987–993.
25. Krishnan L, Karpagaselvi K, Kumarswamy J, Sudheendra US, Santosh KV, Patil A. Inter- and intra-observer variability in three grading systems for oral epithelial dysplasia. *J Oral Maxillofac Pathol*. 2016;20(2):261–268.
26. Warnakulasuriya S, Reibel J, Bouquot J, Dabelsteen E. Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. *J Oral Pathol Med*. 2008;37(3):127–133.
27. Geetha KM, Leeky M, Narayan TV, Sadhana S, Saleha J. Grading of oral epithelial dysplasia: points to ponder. *J Oral Maxillofac Pathol*. 2015;19(2):198–204.
28. Manchanda A, Shetty DC. Reproducibility of grading systems in oral epithelial dysplasia. *Med Oral Patol Oral Cir Bucal*. 2012;17(6):e935–942.
29. Tilakaratne WM, Sherriff M, Morgan PR, Odell EW. Grading oral epithelial dysplasia: analysis of individual features. *J Oral Pathol Med*. 2011;40(7):533–540.
30. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med*. 2016;45(3):155–166.
31. Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ. Oral precursor lesions and malignant transformation—who, where, what, and when? *Br J Oral Maxillofac Surg*. 2015;53(9):831–835.