

Pre-neoplastic lesions of the larynx

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Introduction

Transition from normal laryngeal epithelium to squamous cell carcinoma (SCC) is related to progressive accumulation of genetic changes leading to a clonal population of transformed epithelial cells. Despite extensive research into these genetic changes in laryngeal carcinogenesis, reliable genetic markers with diagnostic and prognostic value are still lacking. The whole spectrum of histological changes occurring in this process has been recently cumulatively designated squamous intraepithelial lesions (SILs), ranging from squamous hyperplasia (SH), to carcinoma *in situ* (CIS) (1).

Histological classifications of laryngeal SILs

Histological classification of laryngeal SILs is the central disputed aspect of these lesions. Regrettably, neither generally accepted criteria nor unified terminology have to date been provided for a histological grading system of laryngeal SILs. In the World Health Organization (WHO) Classification of Head and Neck Tumours, dysplasia system is presented as the 2005 WHO classification simultaneously with the classification of squamous intraepithelial neoplasia (SIN) system and the Ljubljana classification (LC) (1, 2). The majority of current classifications, such as the dysplasia system (2, 5, and 6), SIN (7) and laryngeal intraepithelial neoplasia (LIN) (8) follow criteria similar to those commonly used for epithelial lesions of the uterine cervix. However, the different aetiology of laryngeal lesions and their particular clinical and histological features require a grading system more appropriate to this region (9). The LC was devised in 1971 to cater to these requirements (10). The LC nominally recognizes four grades, and from the prognostic point of view, three categories: SH and basal/parabasal cell hyperplasia (BPH) are classified as benign lesions with a minimal risk of malignant alteration, atypical hyperplasia or risky epithelium (AH) as potentially, and CIS as actually malignant lesion. The main features by which the proposed grading system differs from other classifications are: the distinction between benign and potentially malignant lesions and the positive separation of CIS from AH (1-4, 11, 12).

Although histological assessment of the dysplasia system and the LC are based on the same architectural and cytological changes (irregular epithelia stratification, loss of polarity of basal cells, increased number of mitoses with atypical mitotic figures, increased number of dyskeratotic cells, cellular and nuclear atypias, increased nuclear-cytoplasmic ratio, increased number and size of nucleoli and hyperchromatism), there is no simple relationship or overlapping between the two grading systems (1, 2). In the dysplasia system, there is difficulty in recognising its earliest manifestations, and no single combination of the above listed histological features allows consistent distinction between hyperplasia and the earliest stages of dysplasia, as well as in attempting rigidly to divide the spectrum of dysplasia into mild, moderate and severe categories. CIS remains separated from severe dysplasia (2). The lack of defined criteria for grading laryngeal dysplasia is an important source of inconsistent and poorly reproducible results (1, 13). The binary system of SIN is designed by specific criteria for precisely gauging grades of SIN into hyperplasia/keratosis, SIN I (low grade) and SIN II (high grade) (14, 15). Compared to the LC, the histological criteria of hyperplasia and SIN I could approximately correspond to the histological criteria of SH and BPH, being considered benign lesions with a minimum risk of malignant transformation. In our opinion, thus, the term neoplasia does not suit lesions with a small risk of malignant alteration. The histological features of SIN II correlate partially with AH and partially with CIS of the LC. Cases of CIS, which fulfil all the required criteria, are very uncommon (1, 11). In these cases, the patient should receive more radical treatment than with the grade of AH. Moreover, in such a case, the search for possible foci of invasive carcinoma is mandatory (1).

One can object that grading SILs is an attempt to impose arbitrary distinct categories of a continually progressing process without naturally and sharply defined borders (13, 16). However, this continuous process, which is of long duration, may eventually stop, regress or progress, depending above all on the influence of various noxious agents causing genetic and, consequently, additional phenotypic changes. When a laryngeal biopsy is performed, the established histological changes still serve at present as the main guidance for clinicians on how to treat the patient, as well as being the most reliable prognostic factor of the biological behaviour of the disease (1).

The LC has been used for more than a quarter of a century and has been found to be more precise for daily diagnostic work than other grading systems (1, 3, 9, 12, 17). However, in spite of the well-defined morphological criteria of the LC, especially in cases of AH, the likelihood of eventual malignant alteration remains enigmatic (1).

Malignant transformation of SILs

The results of 10 studies of malignant transformation of laryngeal SILs, vary considerably for each particular grade, as follows: group of SH and KWA from 0% to 4.1%; group of mild dysplasia, SIN I and LIN I from 0% to 11%; group of moderate dysplasia, SIN II and LIN II 4% to 24%; group of severe dysplasia, SIN III, LIN III and ATH from 9 % to 57% (1, 5 - 7, 18-23). The most prominent discrepancy of results appears in the third group, mostly because severe dysplasia and CIS are combined into a single category in numerous studies. The most crucial factor for malignant transformation is certainly an unchanged lifestyle, including failure to give up smoking and drinking alcohol. A correctly performed biopsy is an important prerequisite for reliable grading of SILs. Appearance of invasive cancer within a few months after diagnosis of precancerous lesions indicates on improper site of the first biopsy (21). This precaution was taken strictly into account in the follow up of the study from Ljubljana. Malignant alterations occurred in 1.1% of patients with SH and BPH, within a period of 1.5 to 21 years. Malignant alteration markedly increased in patients with AH to 9.5% within a period of 2-24 years. These results justify the proposal of the Ljubljana classification for dividing the morphological criteria into two basic groups: benign (SH and BPH) and potentially malignant (AH) (1).

Conclusion

There is no general agreement about terminology and histological classification of laryngeal SILs. Data from follow-up studies are hard to compare due to different morphological criteria used for classifying SILs. Additional research work in the field of molecular biology could provide the basis for a single classification of laryngeal SILs (1).

References

1. Gale N, Michaels L, Luzar B et al. Current review on squamous intraepithelial lesions of the larynx.. *Histopathology* 2009; 54; 639-656.
2. Gale N, Pilch BZ, Sidransky D et al. Epithelial precursor lesions. In: Barnes L, Eveson JW, Reichart P, Sidransky D eds. *World health organization classification of tumours. Pathology and genetics of head and neck tumours*. Lyon: IARC, 2005; 140-143.
3. Gale N, Zidar N. Benign and potentially malignant lesions of the squamous epithelium and squamous cell carcinoma. In: Cardesa A, Sliotweg P, eds, *Head and neck, soft tissues, retroperitoneum and skin*. Berlin: Springer, 2006; 1-38.

4. Kambič V, Gale N. Significance of keratosis and dyskeratosis for classifying hyperplastic aberrations of laryngeal mucosa. *Am. J. Otolaryngol.* 1986; 7; 323-333.
5. Hellquist H, Lundgren J, Olofsson J. Hyperplasia, keratosis, dysplasia and carcinoma in situ of the vocal cords - a follow-up study. *Clin. Otolaryngol.* 1982; 7; 11-27.
6. Blackwell KE, Fu YS, Calcaterra TC. Laryngeal dysplasia. A clinicopathologic study. *Cancer* 1995; 75; 457-463.
7. Crissman JD, Visscher DW, Sakr W. Premalignant lesions of the upper aerodigestive tract: pathologic classification. *J. Cell Biochem. Suppl.* 1993; 17F: 49-56
8. Friedmann I, Ferlito A (1993) Precursors of squamous cell carcinoma. In: Ferlito A ed. *Neoplasms of the larynx*, pp 97-111, Churchill Livingstone, Edinburgh
9. Hellquist H, Cardesa A, Gale N et al. Criteria for grading in the Ljubljana classification of epithelial hyperplastic laryngeal lesions. A study by members of the Working group on Epithelial Hyperplastic Laryngeal Lesions of the European Society of Pathology. *Histopathology* 1999; 34; 226-233.
10. Kambič V, Lenart I. Notre classification des hyperplasies de l'épithélium du larynx au point de vue pronostic. *J F O R L* 1971; 20; 1145-1150.
11. Kambič V, Gale N. *Epithelial hyperplastic lesions of the larynx*. Amsterdam: Elsevier, 1995; 1-265.
12. Gale N, Kambič V, Michaels L et al. The Ljubljana classification: a practical strategy for the diagnosis of laryngeal precancerous lesions. *Adv. Anat. Pathol.* 2000; 7; 240-251.
13. Bosman FT. Dysplasia classification: pathology in disgrace? *J. Pathol.* 2001; 194; 143-144.
14. Crissman JD, Sakr WA. Squamous intraepithelial neoplasia of the upper aerodigestive tract. In Gnepp DR ed. *Diagnostic surgical pathology of the head and neck*. Philadelphia: W.B. Saunders, 2000; 1-17.
15. Sakr WA, Gale N, Gnepp DR. Squamous intraepithelial neoplasia of the upper aerodigestive tract. 2nd ed. In Gnepp DR ed. *Diagnostic surgical pathology of the head and neck*. Philadelphia: W.B. Saunders, 2009; in press.
16. Kujan O, Oliver RJ, Khattab A al. Evaluation of binary system of grading oral epithelial dysplasia for prediction of malignant transformation. *Oral Oncol.* 2006; 42; 987-993.
17. Chatrath P, Scott IS, Morris LS et al. Aberrant expression of minichromosome maintenance protein-2 and Ki67 in laryngeal squamous epithelial lesions. *Br. J. Cancer* 2003; 89; 1048-1054.
18. Velasco JRR, Nieto CS, de Bustos CP, Marcos CA. Premalignant lesions of the larynx: pathological prognostic factors. *J. Otolaryngol.* 1987; 16; 367-370.
19. Olde Kalter P, Lubsen H, Delemarre JFM et al. Squamous cell hyperplasia of the larynx. A clinical follow-up study. *J. Laryngol. Otol.* 1987; 101; 579-588.
20. Sllamniku B, Bauer W, Painter C et al. The transformation of laryngeal keratosis into invasive carcinoma. *Am. J. Otolaryngol.* 1989; 10; 42-54.
21. Gallo A, de Vincentiis M, Della Rocca C et al. Evolution of precancerous laryngeal lesions: a clinicopathologic study with long-term follow-up on 259 patients. *Head Neck.* 2001; 23; 42-47
22. Ricci G, Molini E, Faralli M et al. Retrospective study on precancerous laryngeal lesions: long-term follow-up. *Acta Otorhinolaryngol. Ital.* 2003; 23; 362-367.
23. Plch J, Pár I, Navrátilová I et al. Long term follow-up study of laryngeal precancer. *Auris Nasus Larynx.* 1998; 25; 407-412.

