# Surface vascular and epithelial anatomy of the vocal folds in leukoplakia and cancer

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**Abstract**

Objective: To investigate the features of the superficial mucosa and microvascular network of the vocal cords in patients with suspected laryngeal cancer using contact endoscopy (CE). Design: A retrospective review of patients with leukoplakia and cancer of vocal cords. Main outcome measure: Fourty-two patients (mean age = 57.2 ±7.6 years), were prospectively evaluated. Eighteen had malignant lesions and 24 had leukoplakia, proven on histologic exam. Eight cancer patients and 8 patients with leukoplakia had bilateral lesions. Therefore, a total of 58 lesions (26 malignant and 32 non-malignant) was found. Contact-endoscopic imaging findings were classified into five types (I to V) based on the features of the mucosal intraepithelial capillary loops. Results: The CE-based intraepithelial papillary capillary loop classification was strongly correlated with the histological findings. Smoking habits didn't significantly differ between patients with unilateral and bilateral lesions. Conclusions: CE imaging of the vocal cord mucosal capillaries may be useful in the early detection of laryngeal cancer and precancerous lesions.

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Vascular and morphological changes of vocal folds in leukoplakia and cancer

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**Results:** The CE-based intraepithelial papillary capillary loop classification was strongly correlated with the histological findings. Smoking habits didn't significantly differ between patients with unilateral and bilateral lesions.

**Conclusions:** CE imaging of the vocal cord mucosal capillaries may be useful in the early detection of laryngeal cancer and precancerous lesions.

**Key words:** Vascular patterns, epithelium, hyperplasia, contact endoscopy, leukoplakia

**Key points:**

1. Leukoplakia is an anatomical term for thick white or grey patches that can be associated with a variety of histological diagnoses ranging from hyperplasia to malignant transformation.
2. According to our findings, malignancy is associated with a single abnormal vascular pattern on the surface of the vocal cords, whereas leukoplakia might be associated with either normal or many abnormal vascular patterns.
3. Capillaries in the surface lamina propria, smaller arteries and veins characterize the vascular microanatomy of human vocal folds.
4. Age may be related to the development of this disease.
5. Two inherent limitations of CE are the inability to detect very early dysplasia and the inability of differentiation of carcinoma in situ from invasive carcinoma.

## 1 INTRODUCTION

Leukoplakia is a macroscopic anatomical term for thick white or grey patches that can be associated with a variety of histological diagnoses ranging from hyperplasia to malignant transformation.[1-4] Endoscopic (white light, WL) examination combined with stroboscopy is currently the ≪main-stream" approach for detecting and assessing vocal fold leukoplakia (VFL) or other vocal fold lesions.[5-7] Andrea et al. described using contact endoscopy to examine the vocal folds and nasal mucosa in the 1990s.[8,9]

The goal of this study was to evaluate distinct vascular patterns in patients with VFL and glottis cancer using contact endoscopy (CE) and see if there were any correlations with histologic abnormalities in the mucosa of the vocal cord.

## 2 MATERIALS AND METHODS

### 2. 1 *Clinical data*

For the purposes of this study, 42 consecutive participants were prospectively recruited: 24 (7 female, 17 male; **Group A** ) had leukoplakia and 18 (4 females and 14 males) had glottic cancer (pT1, n=6; p T2, n=8; pT3, n=8; **Group B** ). Regarding the patients with malignancies, 8 had bilateral lesions and thus 26 malignant lesions were totally detected by narrow band imaging. Between patients with non-malignant lesions ,8 of them had bilateral lesions of the vocal cords, therefore we have examined a total of 32 nonmalignant lesions. Regarding basic characteristics, there was no difference in age, number of cords affected, cigarettes smoked per year and years smoking between male and female patients (**Table 1** ). For the purposes of our study we have also examined 42 non-smokers (Control Group-**Group C** ), who received total anesthesia for surgeries, such as hernias, colectomies etc, which had nothing to do with otolaryngological diseases..

### 2.2 *Contact endoscopy*

For contact endoscopy the Andrea-Dias Contact Micro Laryngoscope (with HOPKINS Straight Forward Telescope 0° and 30°, with diameter 5.5 mm, length 23 cm, magnification 60 × and 150×); a 3 chip camera (Tricam SL II); a Xenon 175 watt light source and a video recording system (AIDA) were used, all manufactured by Karl Storz, (Tuttlingen, Germany).

The entire larynx was initially visualized with standard white light, followed by visualisation using the narrow band imaging (NBI) mode. Endoscopically guided biopsy of laryngeal lesions was also performed; tissue was fixed in 10% formalin for histological analysis.[10,11] The recorded findings were examined by two persons (PP and VST), who evaluated separately the pictures before discussing together the results. All of them were blinded to the histological results. The interrater reliability was also calculated with the use of Kappa test was estimated at 0.89 (Cohen's kappa statistic).

### 2.3 *Morphological types of the surface of the vocal cords*

The morphological types of vocal fold leukoplakia assessed by preoperative rigid laryngoscopy were categorized as: flat and smooth, elevated and smooth, and rough type.[11]

The definition is presented as the following:

**Flat and smooth type:** Surface: smooth; Margin: lesion without raised margins, being continuous with the surrounding mucosa; Texture: homogeneous, regular, the lesion with even coloration.

**Elevated and smooth type:** Surface: smooth; Margin: lesion with raised margins, sharply demarcated from the surrounding mucosa; Texture: homogeneous, regular, the lesion with even coloration.

**Rough type: Surface:** wrinkled, corrugated; Margin: lesion with raised margins, sharply demarcated from the surrounding mucosa; Texture: non-homogeneous, irregular, the lesion with uneven coloration and is usually accompanied with erosion or ulceration.

2.4 *Patterns and changes*

The Ni categorization was used for the purposes of our research.[12] Intraepithelial capillary loop alterations seen with Contact Endoscopy (CE) can be categorized into five categories (I to V) according to this classification. Intraepithelial papillary capillary loops are nearly inconspicuous in type I, while oblique and arborescent capillaries of small diameter are discernible. The intraepithelial papillary capillary loops are nearly invisible in type II, while the diameter of the clearly apparent oblique and arborescent capillaries is increased. The mucosa is white in type III, and the intraepithelial papillary capillary loops are invisible; if the white patch is thin, the oblique and arborescent vessels can be seen indistinctly, but if the white patch is thick, the vessels are obscured. The mucosal intraepithelial papillary capillary loops appear as scattered, small, dark brown spots in type IV, with a relatively regular arrangement and low density; the capillary terminals are bifurcated or slightly dilated, and the intraepithelial papillary capillary loops appear as scattered, small, dark brown spots; the oblique and arborescent vessels are usually not visible.[12]

**Type V** changes are subdivided into **types Va, Vb** and**Vc** according to the shape, regularity and distribution of vessels. In type Va, intraepithelial papillary capillary loops are significantly dilated and of relatively high density, and appear to be solid or to have hollow, brownish, speckled features and various shapes.[12] In type Vb, the intraepithelial papillary capillary loop itself is destroyed, with its remnants presenting in a snake-, earthworm-, tadpole- or branch-like shape, and the microvessels are dilated, elongated and 'woven' in appearance. In type Vc, the lesion surface is covered with necrotic tissue, and the intraepithelial papillary capillary loops present as brownish speckles or tortuous shapes of uneven density which are irregularly scattered on the tumor surface.[12]

According on the shape, regularity, and distribution of vessels, type V changes are split into types Va, Vb, and Vc. Intraepithelial papillary capillary loops in type Va are highly dilated and of relatively high density, appearing solid or hollow, brownish, speckled, and of varied shapes.[12] The intraepithelial papillary capillary loop is disrupted in type Vb, with remains resembling a snake, earthworm, tadpole, or branch, and microvessels that are dilated, elongated, and 'woven' in appearance. The lesion surface is coated with necrotic tissue in type Vc, and the intraepithelial papillary capillary loops appear as brownish speckles or sinuous shapes of uneven density spread irregularly on the tumor surface.[12,13] Type is depicted in**Images 1, 2,** and **3** .

2.5 *Histologic examination*

All the tissues were processed for pathological testing on a regular basis. The same pathologist evaluated and graded histologically graded formalin-fixed and paraffin-embedded slides independently. Squamous cell hyperplasia with non-dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, and squamous cell carcinoma were all assessed histologically according to the World Health Organization's 2017 guidelines.[14] The new WHO 2017 classification is a two-tier system. Laryngeal precursor lesions are classified as low-grade dysplasia (previous categories squamous hyperplasia, mild dysplasia), and high-grade

dysplasia (previous categories of moderate and severe dysplasia, carcinoma in situ).[14] Carcinoma in situ, is distinguished from high-grade dysplasia, showing features of conventional carcinoma.[14]

### 2.6 *Statistical analysis*

Parameters were evaluated using the Jamovi project (2021; Jamovi, software Version 1.6, Sydney, Australia. Retrieved from www.jamovi.org). A p-value less than 0.05 was considered statistically significant for all analyses. Independent samples t-test, Mann-Whitney U test and Chi square test were used for basic characteristics' comparisons between male and female patients' features (age, years of smoking, number of cigarettes/day) as well as for comparisons between patients with unilateral or bilateral lesions and patients with or without histologically confirmed malignancies. The ANOVA and the nonparametric Kruskal-Wallis tests were used to detect possible statistically significant differences between lesions with different vascular patterns.

## 3 RESULTS

### 3.1 *Smoking status and age between patients with unilateral and bilateral lesions*

The number of cigarettes smoked per day didn't appear significantly different between patients with unilateral and bilateral lesions (U = 56.9, p = .109 and though it seemed to be higher in the malignancies group, that was not statistically significant (U = 56, p = .064). The years of smoking were found to be similar between patients with unilateral and bilateral lesions (t = 0556, p = .956) and although patients who developed malignancies reported having smoked for more time, there was no significant difference when comparing their years of smoking with those of the patients with non-malignant lesions (t = -1.24, p = .227). It was age however that was found to be of true importance, since in our group malignancies were identified in older rather than younger subjects (t = -2.23, p = .034), but that was not observed as regards the bilateral presence of lesions (t = -0.98, p = .332). **Table 2** presents the comparison of smoking status and age between patients with and without malignancies.

### 3.2 *Smoking habits and age in different types of vascular classification*

Moreover, a Kruskal-Wallis test showed no significant statistical difference in cigarettes smoked per day between lesions that had different types of intraepithelial papillary capillary loop classification, $\chi 2$ (5) = 9.93, p = .077 (**Figure 1** ). No such difference was found in years smoking either, as determined by a one-way ANOVA that was also performed, F (5, 9.95) = 2.52, p = .100. Age however presented a significant effect regarding the vascular classification, F (5, 12.9) = 3.71, p = .027. Post-hoc comparisons using the Games-Howell test showed significant difference particularly between the age of patients in the group of type I lesions (M = 52.7, SD = 1.15) and the age in the group of type Vb lesions (MD = 63.7, SD = 8.50). Our results suggest that malignancies had significantly higher chances of developing in older individuals, when compared to the mildest type I lesions of vascular classification.

### 3.3 *Smoking habits and age in different types of morphological classification*

A Kruskal-Wallis test showed no significant statistical difference in cigarettes smoked per day between different types of morphological classification, $\chi 2$ (5) = 4.84, p = .089. In the same way a one-way ANOVA did not indicate statistical difference in the years smoking either F (2, 14) = 2.02, p = .170. Age, according to a one-way ANOVA, was significantly different among different types of morphological classification types, F (2, 35) = 7.72, p = .002. The significant difference in age was detected between the "flat and smooth" type of lesions (M = 51.4, SD = 6.33),p=.002 and the "rough" type of lesions (M = 61.5, SD = 6.83), p = .001 as indicated by post-hoc comparisons using the Tukey correction. The results are depicted in **Table 3** .

### 3.4 *Classification of leukoplakia and smoking habits*

As mentioned above we have examined a total of 32 vocal cords with leukoplakia. By 22 of them a low-grade dysplasia has been found. The rest of them have been diagnosed with a high-grade dysplasia. A Kruskal-Wallis test showed no significant statistical difference in cigarettes smoked per day between different types of morphological classification, $\chi 2$ (5) = 4.64, p = .088. In the same way a one-way ANOVA did

not indicate statistical difference in the years smoking either F (2, 08) = 2.02, p = .1640. The application of Kendal-tau criterion has shown the grade of dysplasia is correlated to age. By patients with low-grade dysplasia (n=18) this was estimated by $\tau$=0.73. By those with high-grade dysplasia (n=14) the correlation was stronger ($\tau$=0.82).

3.5 *Contact Endoscopy in non-smoking and smoking subjects*

We also tested if there was statistical significance between the vascularization type of the vocal cords of the healthy subjects (control group) and the vascularization type of patients suffering from leukoplakia and malignancy. Vocal cords with type I or type II vascularization pattern were more likely to belong to patients who have non-malignant contralateral vocal cords, whereas healthy cords of type III or IV were more likely to be associated with contralateral malignancies, according to a Fisher's exact test that showed statistical significance, p = .002. In non-smoking subjects we have found that 18 of them had a type I vascularization. By the rest a type II vascularization on both sides has been documented.

## 4 DISCUSSION

According to our findings, malignancy is associated with a single abnormal vascular pattern on the surface of the vocal cords, whereas leukoplakia might be associated with either normal or many abnormal vascular patterns. In addition, we discovered that in patients with leukoplakia, the length of time spent smoking (in years) had a detrimental impact on the surface and vascularization of the voice cords. The number of cigarettes smoked each day did not seem to make a difference.

Capillaries in the surface lamina propria, smaller arteries and veins, as well as arterioles and venules in the deeper layers, characterize the vascular microanatomy of human vocal folds. Arterioles and venules have direct vascular anastomoses.[15]

Under rigid laryngeal endoscopy, vocal cord leukoplakia presents as a white or grayish confined patch, distributed granule, or verrucous structure. It may have one or more localizations.[10]Leukoplakia is a chameleon-like epithelial transformation that can range from benign thickening to malignant tumors. As a result, the name "leukoplakia" is insufficient to characterize the lesion's histological identity.[10-13]

There are previous reports on a tissue-specific classification of vascular changes associated with laryngeal leukoplakia. They finally have found that age, non-homogenous lesion texture and existence of hyperemia are independent predictors of malignancy.[14-16] Their results support the findings of the present study to some extent because they also have found that age and lesion texture may predict prognosis. However, these authors have not further explored the impact of age on leukoplakia lesions. Our study provides evidence that age may be related to the development of this disease. Moreover, a further novelty of the present study is that a very detailed study on the lesion texture has been conducted. Leukoplakia lesions have traditionally been divided into two categories from their appearances which were individually homogenous and heterogeneous in many reports.[17]

Although new endoscopic tools, such as narrow band imaging, optical coherence tomography and contact endoscopy have been developed to improve the diagnosis of vocal fold leukoplakia, WL laryngoscopy is most applied in clinical practice.[18-21] The ability of rigid or flexible laryngoscopy to visualize and characterize lesions of vocal cords continues to improve.

Many researchers have reported high efficacy of CE in diagnosis of mucosal lesions not only of larynx, but in other sites of head and neck as well.[10,12,23-25] These results have been obtained taking the histopathological examination as the gold standard. However, the technique of CE has definite advantages and limitations. Contact endoscopy enables visualization of tumor margins, dysplasia, and normal epithelium, thus offering the possibility of more precise complete removal of laryngeal lesions in a single sitting. Along with in vivo studies, contact endoscopy can also be used to analyze the excised segment of the lesion and hence ensure whether the lesion has been completely resected. The grade of dysplasia is indicated by the impaired nucleus/cytoplasm ratio, nuclear hyperchromasia, and variation in the number and appearance of the nucleoli.[21,23]

Of course, there are limitations in the use of CE, which should be also considered in the interpretation and validation of the results of the present study. Two inherent limitations are the inability to detect very early dysplasia and the inability of differentiation of carcinoma in situ from invasive carcinoma.

## 5 CONCLUSION

Vascular changes may play an important role as one of the most prominent features in endoscopic work-up of laryngeal lesions. Further validation of our preliminary findings, especially in combination with further standardized morphologic endoscopy findings (together with macroscopic appearance, mucosal vibration, vocal cord stiffness and others) should be undertaken to increase reliability of pre- and intraoperative diagnosis of leukoplakia and malignant glottic lesions.

## LEGENDS

**Table 1.** Comparison of demographic features between patients with malignant and non-malignant lesions. **Information on s** moking status (cigarettes per day and years smoking) and age in different types of vascular classification is also provides.

**Table 2.** Smoking status (cigarettes per day and years smoking) and age in different types of vascular classification.

**Table 3** . Smoking status (cigarettes per day and years smoking) and age in different types of morphological classification. The meanings of the abbreviations are the following: fs = Flat and smooth type: Surface: smooth; Margin: lesion without raised margins, being continuous with the surrounding mucosa; Texture: homogeneous, regular, the lesion with even coloration; es=elevated and smooth type: Surface: smooth; Margin: lesion with raised margins, sharply demarcated from the surrounding mucosa; Texture: homogeneous, regular, the lesion with even coloration; r = Rough type.

**Images 1, 2** and **3.** The figures depict type I, II and III patterns of vascularization correspondingly. In type I, the intraepithelial papillary capillary loops are almost invisible; oblique and arborescent vessels of small diameter can be clearly seen. In type II, the intraepithelial papillary capillary loops are also almost invisible, but the diameter of the clearly observed oblique and arborescent vessels is enlarged. In type III, the mucosa is whitish and the intraepithelial papillary capillary loops cannot be seen; if the whitish patch is thin, the oblique and arborescent vessels may be seen indistinctly, but if the whitish patch is thick the vessels will be obscured.

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