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Jasmina Stojanović[1,2], Dragan Milovanović[3], Slobodanka Mitrović[4], Andra Jevtović[1,2], Natalija Božović[1,2], Marina Jovanović[1,2], Sunčica Srećković[5,♣], Branislav Belić[1,2]

Videolaryngostroboscopy in early vocal fold carcinoma diagnosis

Ендовидеостробоскопија у раној дијагностици карцинома гласница

[1]University of Kragujevac, Faculty of Medical Sciences, Department of Otorhinolaryngology, Kragujevac, Serbia;
[2]Kragujevac Clinical Center, Clinic of Otorhinolaryngology, Kragujevac, Serbia;
[3]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia;
[4]University of Kragujevac, Faculty of Medical Sciences, Department of Pathology Kragujevac, Serbia;
[5]University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Ophthalmology

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♣**Correspondence to:**
Sunčica SREĆKOVIĆ
Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovića 69, 34000 Kragujevac, Serbia
E-mail: **sunce.sun@yahoo.com**

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SUMMARY

Introduction/Objective Vocal folds are the most common primary site of laryngeal carcinoma. Advancement in diagnostic and therapeutic modalities have provided better prognosis for patients with early glottic carcinoma. We aimed to report the role of videolaryngostroboscopy (VLS) in early diagnosis of vocal fold carcinoma.

Methods Prospective controlled study included 300 dysphonic patients admitted to the tertiary medical center for microlaryngoscopy with biopsy. All patients underwent stroboscopic examination prior to biopsy. VLS findings were classified according to Hirano into 4 stages, with a adynamic vocal fold segment and absence of vocal fold vibration, suspected for vocal fold carcinoma as a stage IV. Histopathological findings have been graded according to Ljubljana classification into simple hyperplasia, abnormal hyperplasia, atypical hyperplasia and carcinoma in situ.

Results Analysis of VLS findings showed that 41.67% of patients (n = 125/300) had asymmetrical and irregular vocal fold vibration with a mucosal wave reduction (VLS stage III) while adynamic vocal fold segment and absence of vocal fold vibration (VLS stage IV), suspected for vocal fold carcinoma, was noticed in 17.33% of patients (n = 52/300). HP report showed that vocal fold carcinoma was verified in 5.6% of patients in VLS stage III (n = 7/125), while in VLS stage IV carcinoma was detected in 26.92% of patients (n = 14/52). Adynamic segment or entire nonvibrating vocal fold finding predicts early glottic carcinoma with a sensitivity of 66.77%, specificity of 86.4%, and moderate diagnostic accuracy (AUC = 0.844).

Conclusion VLS plays an important role as a timely indicator for microlaryngoscopy with biopsy in diagnosis of vocal fold carcinoma.

Keywords: videolaryngoscopy; vocal fold carcinoma; microlaryngoscopy

САЖЕТАК

Увод/Циљ Гласнице представљају најчешћу примарну локализацију ларингеалног карцинома. Напредак у дијагностици и терапији омогућио је бољу прогнозу за пацијенте са раним карциномом глотиса. Основни циљ нашег истраживања је да укажемо на значај ендовидеостробоскопије у раној дијагностици карцинома гласница.

Методе У проспективну контролисану студију укључено је 300 пацијената са дисфонијом, хоспитализованих у терцијарној медицинској установи ради микроларингоскопије са биопсијом. Код свих пацијената учињен је ендовидеостробоскопски преглед пре биопсије. Анализа ендовидеостробоскопског налаза је класификована према Хирану у четири стадијума, тако да адинамични сегмент и одсустне вибрације гласнице представља стробоскопски налаз IV, суспектан за карцином гласнице. Према Љубљанској класификацији, хистопатолошки налаз подељен је на једноставну, абнормалну и атипичну хиперплазију и карцином *in situ*.

Резултати Анализа ендовидестробоскопског налаза показала је да код 41,67% пацијената (*n* = 125/300) постоје обострано присутне асиметричне и ирегуларне вибрације гласница, јако редукованог мукозног таласа (стробоскопски налаз III), док је код 17,33% (*n* = 52/300) пацијената уочен адинамични сегмент и одсутне вибрације гласнице (стробоскопски налаз IV), суспектан на карцином гласнице. Хистопатолошком анализом, карцином гласница је верификован код 5,6% са стробоскопским налазом III (*n* = 7/125) и код 26,92% пацијената са стробоскопским налазом IV (*n* = 14/52). Налаз адинамичног сегмента и одсутних вибрација гласница има сензитивност 66,77% и специфичност 86,4% у детекцији карцинома гласница, са умереном дијагностичком прецизношћу (*AUC* = 0,844).

Закључак Ендовидеостробоскопија игра важну улогу у правовременој индикацији за микроларингостробоскопију са биопсијом у дијагностици карцинома гласница.

Кључне речи: ендовидеостробоскопија; карцином гласница; микроларингостробоскопија

INTRODUCTION

Laryngeal cancer accounts for 30% to 40% of malignant head and neck tumors and 1% to 2.5% of all malignancies. Squamous cell carcinoma adds up to 95% to 98% of laryngeal cancers. The occurrence of laryngeal carcinoma is more common in male patients between the fifth and seventh decades of life. Laryngeal carcinomas are one of several oncological diseases in which the five-year survival rate has decreased from 66% to 63% over the last 40 years, although the total incidence is reducing [1, 2, 3]. In Serbia laryngeal carcinomas are one of the most common malignancies, and according to 2017 data, they rank sixth in terms of occurrence [4].

The first clinically manifested symptom of vocal fold carcinoma is dysphonia. According to American Academy of Otorhinolaryngology and Head and Neck Surgery guidelines, dysphonia diagnostics includes anamnesis, clinical examination focusing on laryngeal motility and visible pathological changes of the vocal folds, videolaryngostroboscopy (VLS) and microlaryngoscopy with biopsy as gold diagnostic standard. The occurrence of vocal fold carcinoma is associated with smoking, gastroesophageal reflux disease, HPV virus, with alcohol being less involved in the development of vocal fold cancer than in other localizations of laryngeal tumors. VLS provides insight in anatomical structures and functional changes of the vocal folds (appearance and vibratory patterns), without complications. Though it is invasive procedure, microlaryngoscopy is necessary complementary method to VLS, and without it histological confirmation of the lesion would be impossible [5, 6, 7].

The aim of this study is to distinguish the presence of early glottic carcinoma in patients with or without dysplastic lesions of vocal folds, using certain clinical characteristics observed during VLS.

METHODS

The prospective study with 300 dysphonic patients was conducted over a four-year period in the Clinic of Otorhinolaryngology, Kragujevac Clinical Center, Serbia. Ethical committee of the Kragujevac Clinical Center, Serbia, approved this study. Patients with functional voice

disorders, benign tumors, pseudotumors, as well as the patients with verified vocal ford carcinoma were excluded from the study. All patients underwent detailed anamnesis, otorhinolaryngological and phoniatric examination, VLS and microlaryngoscopy with biopsy. All subjects gave their informed consent for participation in the study and ethical guidelines of the Declaration of Helsinki were followed during the study.

VLS was performed using a rigid Karl Storz stroboscope (Karl Storz SE & Co. KG, Germany). One doctor performed and evaluated all stroboscopic examinations. Following parameters were analyzed: glottic occlusion, amplitude and regularity of vocal fold vibration and presence of mucosal wave. VLS findings were classified according to Hirano into 4 stages: 1. insufficient glottic occlusion with symmetrical, regular vocal fold vibration with regular amplitude and presence of mucosal wave; 2. insufficient glottic occlusion with symmetrical and regular vocal fold vibration with a reduced amplitude, and slightly reduced mucosal wave; 3. Insufficient glottic occlusion with asymmetrical and irregular vocal fold vibration with a mucosal wave reduction; 4. adynamic vocal fold segment and absence of vocal fold vibration, suspected for vocal fold carcinoma [5, 8].

Microlaryngoscopy with biopsy was performed in general anesthesia with SOM 62 microscope (Karl Kaps GmbH & Co. KG, Germany) and Karl Storz laryngoscope (Karl Storz SE & Co. KG, Germany). All sections of the obtained samples had been embedded in paraffin wax, cut at 3-5 mm thickness from at least two parts of the paraffin block and stained with hematoxylin and eosin for histopathological (HP) analysis. HP findings have been graded according to Ljubljana classification into simple hyperplasia (benign spinous layer augmentation), abnormal hyperplasia (benign basal and parabasal layer augmentation), atypical hyperplasia (risky for malignancy) and *carcinoma in situ*. [9, 10].

The data were analyzed using statistical package SPSS, version 21. The normality of distribution was tested by the Kolmogorov–Smirnov test. The statistical association was evaluated using the Chi-square test. ROC curve is used for the assessment of VLS diagnostic values. Diagnostic value is tested using clinical variables of interest by the method of logistic regression. Diagnostic value of VLS was evaluated through determination of sensitivity, specificity, and diagnostic accuracy. The results were considered significantly different when $p < 0.05$.

RESULTS

Our study included 220 male (73.33%) and 80 female patients (26.67%), with an average age of 50.59 years. The smokers accounted for 88.67% (n = 266/300) of patients, with a 23.970 ± 12.651 mean smoking years history, while 11.33% (n = 34/300) of patients were non-smokers.

Analysis of VLS findings according to Hirano classification showed that all patients had insufficient glottic occlusion. In 27.33% of patients (n = 82/300) we noticed symmetrical, regular vocal fold vibration with regular amplitude and presence of mucosal wave (VLS stage I), 13.67% of patients (n = 41/300) had symmetrical and regular vocal fold vibration with a reduced amplitude, and slightly reduced mucosal wave (VLS stage II) while 41.67% of patients (n = 125/300) had asymmetrical and irregular vocal fold vibration with a mucosal wave reduction (VLS stage III). Adynamic vocal fold segment and absence of vocal fold vibration (VLS stage IV), suspected for vocal fold carcinoma, was noticed in 17.33% of patients (n = 52/300) (Table 1).

All patients underwent microlaryngoscopy with vocal fold biopsy. HP report showed that simple hyperplasia was present in 42% of patients (n = 126/300), abnormal hyperplasia in 28.67% of patients (n = 86/300), 22.33% of patients (n = 67/300) had atypical hyperplasia, while 7% of patients (n = 21/300) was diagnosed with laryngeal carcinoma (Table 1).

In VLS stage I most common HP finding was simple hyperplasia. Carcinoma was not detected in VLS stages I and II. In VLS stage III carcinoma was verified in 5.6% of patients (n = 7/125), while in VLS stage IV carcinoma was detected in 26.92% of patients (n = 14/52) (Figure 1a, b). HP reports indicating carcinoma showed that 52.38% of patients (n = 11/21) had *carcinoma in situ*, while 47.62% of patients (n = 10/21) had invasive laryngeal carcinoma. Our results showed that in VLS stage IV was significantly more patients with carcinoma comparing to other VLS stages (Figure 1b).

To examine diagnostic significance of VLS in carcinoma diagnostics we used ROC curve for determination of procedure sensitivity and specifity, univariate and bivariate logistic regression. Adynamic segment finding had 0.667 sensitivity and 0.864 specificity in detection of vocal fold carcinoma (AUC = 0.844, 95% CI 0.772-0.916). Odds ratio for VLS findings of

3.44 (95% CI 2.14-5.51) indicates that for each gradation of findings, from VLS stage I to stage IV, chance for carcinoma detection after biopsy is increased. Our results imply a cutoff point for early diagnostics of glottic carcinoma with a sensitivity of 66.77%, specificity of 86,4%, and moderate diagnostic accuracy (AUC = 0.844) for early detection of glottic carcinoma. According to our results, VLS predicts most precisely early glottic carcinoma when adynamic segment or when entire nonvibrating vocal fold is found (Figure 2).

DISCUSSION

There is a great interest in the assessment of the VLS role in diagnosis of vocal fold carcinoma and benign pathology [9, 10]. VLS is considered to be an objective method with a subjective interpretation of the experienced endoscopists [5, 11]. In our study, VLS was used as a diagnostic procedure, while biopsy with HP evaluation as a gold diagnostic standard was a comparative method used to confirm stroboscopic prediction.

Analyzing the VLS and HP reports of 112 subjects, Jotic et al. [5] found that the adynamic segment was present in 15.1% of patients with mild, 38.5% of patients with moderate and in 54.5% of patients with severe dysplasia (carcinoma in situ). In a prospective clinical trial of 66 patients VLS findings were compared with histopathological verification of glottic carcinoma. Asymmetrical and irregular vocal fold vibrations with absent mucosal wave or absent vibrations of one part or the entire vocal fold were histopathologically confirmed as cancer in 85% of patients. There were 7 HP reports positive on carcinoma (87.5%) and 1 negative (12.5%) in the group of patients with absent mucosal wave. In the group of patients with absent vocal fold vibrations, there were 49 positive (84.48%) and 9 negative (15.52%) HP reports. The authors concluded that in the cases of hoarseness present more than 14 days, VLS is the method of choice in assessing the need for microlaryngoscopy and HP verification [12]. El-Demerdash et al. [13] found that the sensitivity and specificity of VLS in predicting the invasive nature of vocal fold lesions based on the absence or reduction of the mucosal wave was 96.8 and 92.8%. Caffier et al. [14] found absence of vocal fold vibrations and adynamic segment (VLS stage IV) in 17/34 patients, while in 16 patients malignancy was histopathologically confirmed. In addition, Gugatshka et al. [15] showed that combination of exfoliative cytology and VLS allows detection of glottic cancer with a sensitivity of 97%. In

compliance with available data, our results showed that 26.92% of the patients (14/52) with adynamic segment and absent vocal fold vibration had histopathologically confirmed vocal fold carcinoma. In addition, in 66.67% of the patients (14/21) with vocal fold carcinoma adynamic segment and absent vocal fold vibration were detected (Figure 1). Adynamic segment or absent vocal fold vibrations predict early glottic carcinoma with a sensitivity of 66.77%, specificity of 86.4%, and moderate diagnostic accuracy, AUC = 0.844 (Figure 2).

Gamboa et al. [16] used the WHO histopathology classification, which is compatible with the Ljubljana classification that we used in our study. Absent mucosal wave as a suspected VLS finding was observed in 15 patients. Severe dysplasia was histopathologically confirmed in 13.4% of the patients (n = 2/15), and planocellular carcinoma in 46.7% (n = 7/15). Histopathology did not show cell atypia in 26.7% of the patients (n = 4/15), while remaining 13.4% (n = 2/15) showed mild dysplasia.

VLS findings that are characteristic of chronic laryngitis (asymmetrical vocal fold vibrations with reduced amplitudes and mucosal wave reduction) demand particular attention because continuous VLS monitoring of these patients allows early diagnosis of vocal fold carcinoma [7, 11, 13, 15, 17].

The recognition of clinical manifestations and exposure to risk factors for the vocal fold carcinoma is important to primary care in order to promptly refer the patient to otorhinolaryngological examination and to establish a timely indication for microlaryngoscopy with biopsy [18–21]. VLS is very important prompt indicator for microlaryngoscopy with biopsy as a gold standard procedure for diagnosis of vocal fold carcinoma. During microlaryngoscopy patient must be under general anesthesia, which makes examination of the larynx mobility impossible [22, 23]. Also, vocal fold scaring after the biopsy is possible as the tissue does not have the ability to regenerate. According to American Academy of Otorhinolaryngology and Head and Neck Surgery guidelines for dysphonia diagnostics, VLS enables good visualization of the larynx which is important before performing microlaryngoscopy [24, 25, 26].

CONCLUSION

Results of this study implicate fundamental significance of VLS in diagnosis of early glottic carcinoma as VLS precisely predicts early glottic carcinoma when adynamic segment or when entire nonvibrating vocal fold is found.

Conflict of interest: None declared.

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Table 1. Number of patients with specific epithelial hyperplastic laryngeal lesions distributed by videolaryngostroboscopy (VLS) stages

Epithelial hyperplastic laryngeal lesions	VLS stages				Total
	Stage I	Stage II	Stage III	Stage IV	
Simple hyperplasia	73	17	33	3	**126 (42%)**
Abnormal hyperplasia	5	17	46	18	**86 (28.67%)**
Atypical hyperplasia	4	7	39	17	**67 (22.33%)**
Carcinoma	0	0	7	14	**21 (7%)**
Total (%)	**82 (27.33)**	**41 (13.67)**	**125 (41.67)**	**52 (17.33)**	**300**

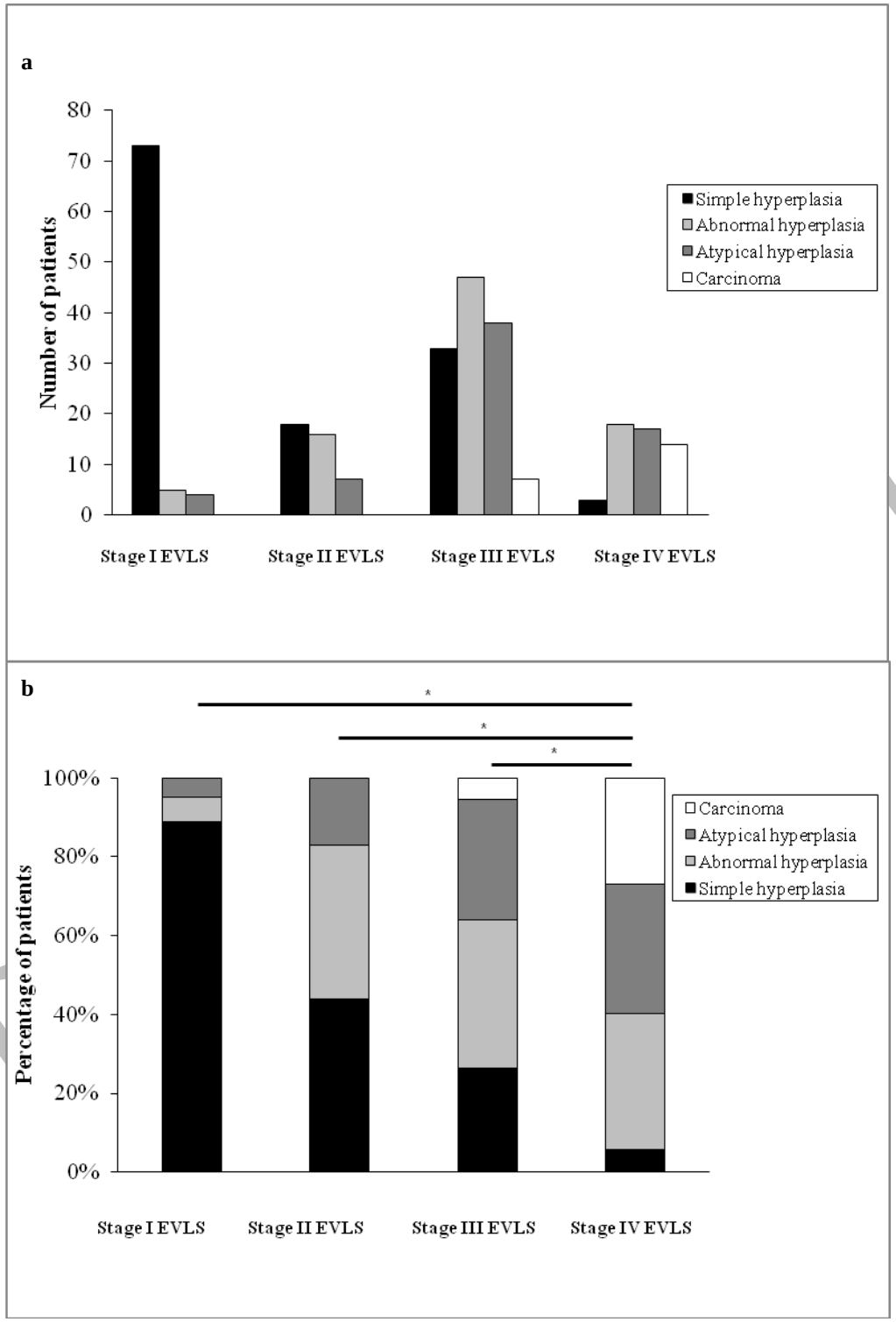

Figure 1. Distribution of epithelial laryngeal lesions according to endovideolaryngostroboscopy (EVLS) findings

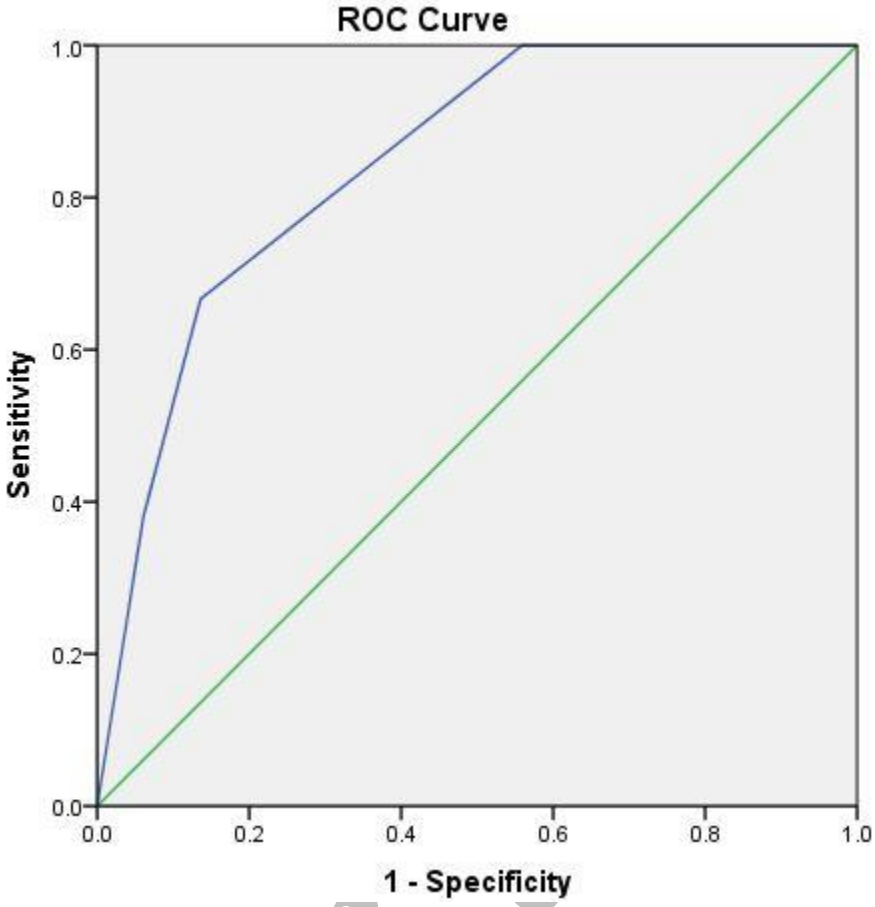

Figure 2. The area under receiver operating characteristic curve for the sensitivity and specificity of videolaryngostroboscopy in vocal fold carcinoma diagnosis

