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WILEY
Diagnostic Accuracy of Narrow Band Imaging in Patients with Oral Lichen Planus: A Prospective Study

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INTRODUCTION

Oral lichen planus (OLP) is a chronic mucocutaneous immune-mediated disease affecting 1% to 4% of the worldwide population. Development of malignant lesions is reported but only affects a minority of patients. The aim of our study was to assess the diagnostic potential of narrow band imaging (NBI) in OLP patients; focusing on the identification of high-grade dysplasia/carcinoma in newly developed lesions.

Objective: Oral lichen planus (OLP) is a chronic mucocutaneous immune-mediated disease affecting 1% to 4% of the worldwide population. Development of malignant lesions is reported but only affects a minority of patients. The aim of our study was to assess the diagnostic potential of narrow band imaging (NBI) in OLP patients; focusing on the identification of high-grade dysplasia/carcinoma in newly developed lesions.

Methods: Prospective evaluation of 56 patients with histopathologic diagnosis of OLP and presenting newly developed lesions not responding to medical treatment. All lesions were assessed by high-definition (HD) white light (WL) and HD-NBI endoscopy. All patients underwent biopsy regardless of the appearance at HD-WL and HD-NBI. Histology was defined as “positive” in case of high-grade dysplasia or carcinoma.

Results: Five lesions (9%) were diagnosed as high-grade dysplasia/carcinoma. In this setting, overall diagnostic potential of HD-NBI was optimal, with a sensitivity of 100% (95% CI, 48–100), specificity of 96% (95% CI, 86–99), negative predictive value of 100% (95% CI, not calculable), positive predictive value of 71% (95% CI, 39–91), and accuracy of 96% (95% CI, 88–100).

Conclusions: Despite the diffuse inflammatory pattern derived from OLP, NBI improved the diagnostic accuracy and the capability to detect high-grade dysplasia/carcinoma.

Key Words: Lichen planus, oral cavity, cancer, carcinoma, NBI, narrow band imaging.

Level of Evidence: 4

Laryngoscope, 00:1–6, 2020

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Disclosure: The authors have no funding or conflicts of interest to declare.

Editor’s Note: This Manuscript was accepted for publication on July 30, 2020.

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DOI: 10.1002/lary.29035

Laryngoscope 00: 2020

Deganello et al.: Narrow Band Imaging in Oral Lichen
On these bases, the aim of the present study is to preliminary assess the diagnostic potential of NBI in patients affected by OLP presenting newly developed suspect lesions, despite the presence of possible confounding factors.

**MATERIAL AND METHODS**

**Study Design**

This prospective study included all patients affected by biopsy-proven OLP with newly developed lesions not responding to medical treatment during follow-up at the Oral Pathology Clinic. The diagnostic accuracy of NBI was evaluated in this specific patient population. The study followed the Standards for Reporting Diagnostic (STARD) accuracy studies recommendations and checklist.17

Data were collected and analyzed in a dedicated database. The study was performed following the principles of the Declaration of Helsinki and was approved by the Research Review Board, Ethics Committee, of the ASST Spedali Civili of Brescia, Italy.

**Participants**

Patients were evaluated at the Unit of Otorhinolaryngology–Head and Neck Surgery of the ASST Spedali Civili, University of Brescia, Brescia, Italy, from January 2009 to October 2018. All patients were referred by the Service of Oral Pathology of the same institution. A total of 586 patients affected by OLP was screened for the study. Figure 1 shows the flow-chart for study inclusion.

Inclusion criteria were:

- Previous diagnosis of OLP (incisional biopsy previously performed at the Oral Pathology Clinic).
- Newly developed suspect lesion not responsive to maximal medical treatment lasting at least 1 month.

**Study Definitions**

The definition of newly developed suspect lesion was: leukoplakia, erythroplakia, erythroleukoplakia, or erosive lesion not present at the previous outpatient evaluation or referred by the patient as recently developed (Fig. 2).

Maximal medical treatment was defined as: topical/ oral corticosteroids, topical/oral antymycotic therapy, topical antiseptic, and topical vitamin E.

No response to medical treatment was defined as the absence of partial/total regression of the lesion and its symptoms, or progression/worsening of the lesion and its symptoms at the 4–6 week follow-up visit. The evaluation was performed in the referral outpatient clinic at the Unit of Otolaryngology by means of high-definition (HD) white light (WL) and NBI endoscopy.

**Test Methods**

The prospective protocol consisted of sequential endoscopic HD oral examinations with WL and NBI, performed by one of three authors with at least 2 years of experience with NBI (A.P., F.D.B, R.M.). All lesions were evaluated by 0-degree rigid telescope coupled to an Evis Exera II HD camera connected to an Evis Exera II CLV-180B/III CV-190 light source (Olympus Medical Systems Corporation, Tokyo, Japan) by both HD-WL and HD-NBI. All exams were video-recorded, stored, and then independently (re)-evaluated by the three authors as positive or negative, separately at WL and NBI.

Examiners were blinded to patients’ notes and clinical history but were informed of the study protocol. Lesions were defined as positive or negative, based on a consensus of two authors; in case of disagreement between the first two authors, a third author provided a further evaluation.

According to the literature and our previous experience, any well-demarcated brownish area with thick dark spots due to abnormal intrapapillary capillary loops (IPCLs) and/or winding vessels was considered as an NBI positive lesion. Mild and diffuse enlargement of IPCLs without clear demarcation was defined as related to inflammation (typical of OLP), as previously described by Takano et al.18

**Histological Examination**

After evaluation, all lesions were biopsied under local anesthesia regardless of the appearance at HD-WL and HD-NBI. Each biopsy was performed focusing on the area with the worse NBI pattern. In case of different independent regions with suspect NBI patterns, a separate biopsy of all areas was performed. Specimens were then submitted to dedicated head and neck surgical pathologists and classified in accordance with the fourth Edition of the WHO classification. Histopathology was defined as “positive” in case of diagnosis ranging from high-grade dysplasia (moderate or severe) to invasive carcinoma. “Negative” lesions included OLP without dysplasia or with low-grade (mild) dysplasia.
Statistical Analysis

Statistical analysis was carried out using STATA 13 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Each lesion was classified according to its appearance under WL and NBI (not suspicious vs. suspicious) and sensitivity (Se), specificity (Sp), positive (PPV), negative predictive values (NPV), and accuracy (Ac) of HD-WL, and HD-NBI were calculated. Interrater reliability was calculated using pairwise Cohen’s Kappa (κ).

In consideration of the exploratory nature of the study and the absence of significant data concerning the use of NBI in this setting, no preliminary power analysis was performed.

RESULTS

Study Population

The study analyzed 56 consecutive patients with a male-to-female ratio of 1:2.6. Most patients (80%) were in their 6th decade or over, with a median age of 68 years (mean, 67; range, 31–88). Among all patients, 19 (34%) were current or former smokers and 6 (11%) were usual alcohol consumers.

The most frequently involved subsites were: buccal mucosa (66%), alveolar ridge (21%), and oral tongue (9%). Macroscopic appearance was: leukoplakia in 43 (77%) patients, erythroleukoplakia in 9 (16%), and erosive lesion in 4 (7%). Considering the entire cohort, 51 lesions (91%) showed no signs of high-grade dysplasia or carcinoma (OLP mucosa in 47 and low-grade dysplasia in 4), while 5 (9%) demonstrated the presence of high-grade dysplasia or carcinoma. In particular, high-grade dysplasia/carcinoma was observed in 2% of leukoplakias, 33% of erythroplakias, and 25% of erosive lesions. All patients (N = 5) with positive histopathology (high-grade dysplasia/carcinoma) were treated by transoral resection. Two of them subsequently developed disease recurrence/second tumors during the follow-up. Both had multiple recurrences along the years (2 and 4, respectively).

Test Results

Forty-nine patients did not show evidence of suspicious lesions at HD-WL evaluation. In 48 (98%) of those,
histopathology was negative (true negatives; Fig. 3), while 1 (2%) was positive for high-grade dysplasia/carcinoma. Seven lesions were considered macroscopically suspicious at HD-WL: 4 (57%) were confirmed as high-grade dysplasia/carcinoma (true positives; Fig. 4), and 3 (43%) were negative at histopathology (false positives). HD-WL showed a sensitivity (Se), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV), and accuracy (Ac) of 80%, 94%, 98%, 57%, and 93%, respectively.

At HD-NBI evaluation, 49 patients (88%) did not present suspicious lesions, all 49 had negative histopathology (true negatives; Fig. 3). Seven patients (12%) showed suspicious lesions at the HD-NBI evaluation: 5 (71%) were positive for high grade dysplasia/carcinoma at histological examination (true positives; Fig. 4) and 2 (29%) were negative (false positives). In the false positive subgroup, 1 lesion was erosive OLP with foci of low-grade dysplasia, and 1 erosive OLP. In terms of interrater reliability, the Kappa coefficient for the HD-NBI evaluation was 0.85. The rate of disagreement between the first two authors evaluating the NBI pattern was 4% (N = 2). NBI showed a Se, Sp, NPV, PPV, and Ac of 100%, 96%, 100%, 71% and 96%, respectively. Results are summarized in Table I.

### DISCUSSION
In the present preliminary study, we confirmed the diagnostic value of NBI in the evaluation of patients with OLP. Its performance was optimal despite the presence of potential confounding factors related to the disease itself (ie, inflammation and erosive lesions), maintaining a satisfying PPV even in this setting. In fact, this technology proved to be effective in the assessment of a selected high-risk population referred to the Otolaryngology Department for newly developed lesions not responding to medical treatment. This selection justifies the relatively high rate of malignant transformation in the present series (9%), that is significantly lower when considering the entire screened population (5/586; 0.9%). Although the World Health Organization (WHO) currently classifies OLP as a precancerous disease, there is considerable controversy regarding its neoplastic potential due to a wide range of malignant transformation rates (0%–14.3%) reported in the literature.4,5,16,19 Some of the controversy can be attributed to: 1) the absence of universally accepted criteria used for diagnosis of OLP, and 2) its complex histopathological diagnosis, with various alterations that can mimic OLP but may present a higher risk of malignant transformation. In fact, the modified World Health Organization (WHO) diagnostic criteria of OLP and oral lichenoid lesion includes the “absence of epithelial dysplasia” as one of the histopathologic criteria. Conversely, the terms “lichenoid dysplasia” and “epithelial dysplastic lesions showing lichenoid features” broadly refer to lesions presenting inflammatory changes similar to OLP but without basal cell degeneration and in presence of epithelial dysplasia. However, differentiation of these clinical and histological definitions may be difficult, and the risk of misclassification is particularly high. In a review of the literature, Krutchkoff et al.20 performed a re-

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**TABLE I.** The Se, Sp, PPV and NPV, and Ac of HD-WL and HD-NBI Examinations for the Entire Cohort of Patients.

<table>
<thead>
<tr>
<th></th>
<th>Se (95% CI)</th>
<th>Sp (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
<th>Ac (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD-WL</td>
<td>80% (28–99)</td>
<td>94% (84–99)</td>
<td>80% (89–100)</td>
<td>57% (29–81)</td>
<td>78% (83–98)</td>
</tr>
<tr>
<td>HD-NBI</td>
<td>100% (48–100)</td>
<td>96% (86–99)</td>
<td>100% (ND)</td>
<td>71% (39–91)</td>
<td>96% (88–100)</td>
</tr>
</tbody>
</table>

Ac = accuracy; CI = Confidence Interval; HD-NBI = high definition narrow band imaging; HD-WL = high definition White light; ND = Not determinable; NPV = negative predictive values; PPV = positive predictive values; Se = sensitivity; Sp = specificity.
evaluation of 223 reported OLP malignant transformations, and concluded that in only 15 cases OLP was likely to be the leading etiopathogenetic factor. Still, no objective data is available from this study, since it was based on subjective evaluations on cases reported by other authors.

For this reason, OLP, oral lichenoid lesions, and oral lichenoid dysplasia are difficult to differentiate and may merely be the tentative categorization of a wide array of immune-related oral alterations. This underlines the risk of misclassification even when the specimen has been analyzed by an experienced dedicated head and neck pathologist. Furthermore, diagnostic biopsies are mostly taken from one or few mucosal spots and are never representative of the whole scenario since a throughout pathological analysis would require excision of large portions of oral mucosal lining which would result in unacceptable overtreatment in most cases.

In this view, patient follow-up should take into account this possible variability in dysplastic/neoplastic potentials, and an initial diagnosis of OLP should not lead to underestimation of progressing or newly developed lesions. Finally, follow-up time is extremely variable among studies evaluating OLP, and sometimes insufficient to significantly assess the true risk of progression. Consequently, there is no clear consensus on the optimal follow-up policy and the value of “optical biopsy” techniques such as NBI.

Interestingly, our patients developing high-grade dysplasia/carcinoma presented different characteristics when compared with conventional oral cancer cohorts: predominance of females, low prevalence of smoking and alcohol abuse. In fact, these differences may be related to an immune-related carcinogenic effect, histopathologically presenting with lichenoid features.

This highlights the need for a standardized classification of immune-related oral lesions aimed at achieving a prognostic stratification according to its risk of progression. In fact, while the vast majority of patients diagnosed with OLP do not progress towards dysplasia or carcinoma, our study shows that a selected number of them may gradually develop dysplastic areas in absence of significant risk factors for oral cancer. In this view, since conventional OLP usually does not present genetic markers associated with dysplasia, these could be employed to identify pre-neoplastic progression in selected high-risk patients.

Finally, there are no widely accepted indications of the ideal follow-up policy of OLP patients. Our study shows that development of a progressive lesion non-responsive to conventional treatment should be regarded as an alarm signal and accurately managed. However, even in this specific scenario, the rate of high-grade dysplasia and malignancy remains low (9%). In this view, NBI has the capability to identify modifications in dimension, shape, and density of the mucosal-submucosal vascular network in order to obtain adjunctive information concerning tumor-related neoangiogenesis. In the last 10 years, a number of different studies confirmed the effectiveness of NBI in early detection of cancer and pre-malignant lesions of the head and neck, with some reports focused on the oral cavity, both in the pre- and postoperative setting. Furthermore, Sekine et al. provided adjunctive proof of the incremental vascular alteration of patients with inflammatory, dysplastic, and neoplastic lesions of the oral cavity, while showing conflicting results in a limited series of patients (N = 18) affected by OLP. In a systematic review on the use of NBI in the oral cavity, Vu and Farah reported a Se, Sp, PPV, NPV, and Ac of 87%–96%, 94%–98%, 73%–96%, 97%–98%, and 92%–97%, respectively. The usefulness of NBI in the diagnosis of oral lesions has been widely demonstrated by our group in the past, not only in the diagnosis of malignant and pre-neoplastic lesions, but also in the follow-up of patients treated with surgery or chemo-radiotherapy/radiotherapy, considering the latter as a confounding factor that did not significantly interfere with NBI evaluation after an adequate training period.

In the present series, application of NBI in the evaluation of lesions arising in OLP confirmed its efficacy in detecting precancerous conditions (high grade dysplasia) and cancer with a Se, Sp, PPV, NPV, and Ac of 100%, 96%, 100%, 71% and 96%, respectively. Furthermore, NBI evaluation showed an optimal interrater reliability even in this setting. It is essential to underline that values of Se, Sp, NPV, and PPV are non-inferior to those present in literature among all the upper aero-digestive tract, despite all perceived confounding factors. In fact, NBI evaluation in the oral cavity is sometimes regarded as less intuitive by the presence of different epithelial types, thick and keratinized mucosal areas, and OLP patients are always burdened by diffuse and significant chronic inflammation that generally leads to abnormal vascular patterns.

Moreover, it should be taken into consideration that patients diagnosed with OLP represent a specific population with higher levels of stress, anxiety, suffering from a pathology that can only be managed by temporary symptomatic drugs, and frequently submitted to multiple biopsies during their lifetimes. In this perspective, the use of NBI can help reduce the number of unnecessary biopsies and the ensuing patient discomfort, reassuring this fragile patient category. In fact, according to our results, in 43% of biopsies performed only on the basis of HD-WL endoscopy, the histological examination turned out to be negative (false positive). In these cases, patients undergo an unnecessary invasive procedure, potentially impacting their quality of life. Furthermore, one patient (2%) presented high-grade dysplasia/carcinoma but was negative at the HD-WL examination. In consideration of the optimal NPV (100%) that we obtained using HD-NBI, many unnecessary biopsies could be avoided and a less intensive follow-up policy could be considered in absence of atypical NBI patterns suggestive for malignancy. In particular, patients with stable disease may be safely followed by regular oral examinations by frontal light. However, these patients should be referred to HD-NBI evaluation in presence of progressive lesions or stable lesions not responding to medical therapy (Fig. 5). In this context, in presence of two consecutive negative HD-NBI evaluations, the patient could safely resume the conventional follow-up without the need for biopsies. This approach proved to be effective in a similar preliminary report by Cozzani et al.
Finally, the following study limitations should be underlined. Patients included in the present series were selected from a general cohort followed at the Oral Pathology Clinic. Therefore, these results may be considered applicable only to subjects with OLP presenting newly developed lesions not-responsive to medical treatment or recent clinical worsening of lesions that remained indolent for a long time. In view of this selection, patient numerosity was low and it was not possible to recruit a validation cohort.

CONCLUSIONS

NBI is a sensitive and an accurate endoscopic tool that allows to effectively detect (pre)-neoplastic areas within the altered mucosa in patients affected by OLP and its high NPV might allow to avoid a biopsy in negative cases. This technology should therefore be considered in the routine follow-up of this complex clinical scenario.

BIBLIOGRAPHY