Oral Oncology 46 (2010) 307–310

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Narrow band imaging and high definition television in evaluation of oral and oropharyngeal squamous cell cancer: A prospective study ☆

C. Piazza [a,*], D. Cocco [a], F. Del Bon [a], S. Mangili [a], P. Nicolai [a], A. Majorana [b], A. Bolzoni Villaret [a], G. Peretti [a]

[a] Department of Otorhinolaryngology – Head and Neck Surgery, University of Brescia, Piazza Spedali Civili 1, 25123 Brescia, Italy
[b] Department of Oral Medicine, Dental Clinic, University of Brescia, 25123 Brescia, Italy

ARTICLE INFO

Article history:
Received 15 January 2010
Received in revised form 27 January 2010
Accepted 27 January 2010
Available online 26 February 2010

Keywords:
Narrow band imaging
High definition television
Endoscopy
Squamous cell cancer
Oral cancer
Oropharyngeal cancer

SUMMARY

Narrow band imaging (NBI) is an optical technique in which filtered light enhances superficial neoplasms based on their neoangiogenic pattern. The accuracy of NBI can be augmented by combining it with high definition television (HDTV). The aim of this study was to prospectively assess the diagnostic value of NBI in combination with HDTV in evaluation of oral (O) and oropharyngeal (OP) squamous cell carcinoma (SCC). Between April 2007 and December 2009, we analyzed 96 patients who were divided into 2 groups: Group A included 35 patients previously biopsied and diagnosed with OSCC or OPSCC and subjected to pre- and intraoperative HDTV white light (WL) and HDTV NBI endoscopy; Group B included 61 subjects already treated for OSCC or OPSCC and followed-up with HDTV WL and HDTV NBI. Fourteen of 35 (40%) patients in Group A showed adjunctive findings with NBI compared to standard WL. All of these findings were histologically confirmed. Twelve of 61 (20%) patients in Group B showed positive NBI findings, which were all confirmed by histology. The sensitivity, specificity, positive, negative predictive values, and accuracy for HDTV WL were 51%, 100%, 100%, 87%, and 68%, respectively, whilst for HDTV NBI were 96%, 100%, 100%, 93%, and 97%, respectively. Overall, 26 of 96 (27%) patients had a diagnostic advantage in applying NBI and HDTV: 6 patients received a diagnosis of recurrence and 1 of persistence after previous treatments; 5 showed a metachronous tumour; in 4 a synchronous tumour was diagnosed; 9 lesions were upstaged; in 1 patient previously diagnosed with an unknown primary by fine needle aspiration cytology on the neck, an anterior tonsillar pillar cancer was identified.

Introduction

Despite advances in the field of cancer detection and therapy, the 5-year survival rate of oral (O) and oropharyngeal (OP) squamous cell carcinoma (SCC) remains below 60%. Although both the oral cavity and oropharynx are easily accessible for self-assessment and clinical examination, early diagnosis is still not commonplace. Therefore, diagnostic delay, along with consequent regional involvement of neck nodes, distant metastases, and the high incidence of upper aerodigestive tract second primary tumours, still represent the main factors that impact the prognosis of OSCC and OPSCC.[1–3]

Proper management of patients with OSCC and OPSCC should always begin with accurate evaluation: visual examination followed by biopsy remains the most widely accepted first diagnostic step. However, the development of a non-invasive method for evaluation of pre-neoplastic and neoplastic changes in the surrounding field of cancerization has the potential to improve both the quality of life and survival rate. Accordingly, in the last two decades, adjunctive techniques such as vital tissue staining, chemiluminescence, and autofluorescence have emerged with the objective of enhancing the assessment of oral and oropharyngeal mucosa, facilitating "*in vivo*" detection and distinguishing between premalignant and malignant lesions.[4]

In this regard, the introduction of narrow band imaging (NBI, Olympus Medical System Corporation, Tokyo, Japan), already proven to be a useful screening method in other medical fields, has recently shown its potential in identifying carcinomas at an early stage in head and neck mucosal sites.[5–9] NBI is an endoscopic technique using narrow-band spectrum optical filters to enhance the visualization of mucosal and submucosal microvascular patterns. The technique is based on the fact that the depth of penetration of light is dependent on its wavelength. The filters used in NBI select blue and green light with wavelengths of 415 and 540 nm, respectively, corresponding to the peaks of absorption of haemoglobin. These filtered wavelengths penetrate the superficial layers of mucosa, thus highlighting the capillary network, and at deeper levels enhance submucosal vessels. In this way, superficial mucosal lesions that would be missed by standard white light (WL)

☆ Presented at the Second World Congress of the International Academy of Oral Oncology, 8–11 July, 2009, Sheraton Centre, Toronto, Canada.

* Corresponding author. Tel.: +39 30 3995319; fax: +39 30 395212.
E-mail address: ceceplaza@libero.it (C. Piazza).

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doi:10.1016/j.oraloncology.2010.01.020

endoscopy, are better identified in view of their neoangiogenic pattern. Additionally, the best image definition for both conventional WL and NBI endoscopy is achieved using a high definition television (HDTV) camera, which provides 1080 lines of resolution, thus allowing a signal definition that is 4.26 times better than standard definition television.

The aim of this paper was to prospectively assess the diagnostic advantages of NBI and HDTV in the pre- and intraoperative diagnostic work-up of untreated patients with biopsy-proven OSCC and OPSCC, as well as in the follow-up of a cohort of subjects previously treated by surgery, radiotherapy (RT) or chemo-RT for the same disease.

Materials and methods

The present not randomized, not blinded, prospective study was conducted between April 2007 and December 2009 at the Department of Otorhinolaryngology – Head and Neck Surgery of the University of Brescia, Italy. A total of 96 patients (58 males, 38 females; mean age, 61.7 years; range, 35–86) affected by biopsy-proven OSCC and OPSCC or previously treated for the same disease underwent endoscopic evaluation with HDTV WL and HDTV NBI. Patients were divided in 2 groups: Group A (staging group), including 35 patients submitted to endoscopic evaluation during the hospitalization period before surgical treatment, and Group B (follow-up group), including 61 subjects endoscopically evaluated at least 6 months after treatment (surgery, RT, or chemo-RT). Among the patients in the latter group, 16 (29%) were evaluated 2 or more times with a minimum interval of 6 months during follow-up.

In Group A, patients were submitted to panendoscopy of the upper aerodigestive tract using a transnasal flexible videoendoscope (ENF-VQ-High Resolution, Olympus Medical Systems Corporation, Tokyo, Japan) under local anaesthesia with 1% oxybuprocaine chlorohydrate. The oral cavity and oropharynx were subsequently evaluated with transoral 0° and 70° rigid endoscopes (Karl Storz, Tuttlingen, Germany) coupled to an Evis Exera II HDTV camera connected to an Evis Exera II CLV-180B light source (Olympus Medical Systems Corporation, Tokyo, Japan) by both WL and NBI. The switching from HDTV WL to HDTV NBI was accomplished by using a fingertip control on the HDTV camera. All examinations were recorded and stored for subsequent re-evaluation. Our attention was focused on the superficial extension of the primary lesion, and special emphasis was given to its margins, extension to surrounding areas, multifocality, and detection of synchronous lesions in order to adequately plan surgical treatment.

According to the literature,[7,9] any well-demarcated brownish area with thick dark spots and/or winding vessels was considered as a "positive" lesion by NBI (Fig. 1A and B).

Under general anaesthesia, before surgical resection, all patients in Group A underwent further intraoperative HDTV WL and HDTV NBI evaluation. Surgical excision was therefore performed taking into account information obtained by HDTV NBI. All excised specimens were oriented, stained with black ink at one surgical margin, and submitted for histopathologic examination to a dedicated pathologist to obtain specific information regarding the "positive" areas identified by HDTV NBI.

Patients in Group B were submitted to panendoscopy with a transnasal flexible videoendoscope and to transoral rigid HDTV WL and HDTV NBI endoscopy under local anaesthesia. In this group, we focused on early detection of persistent or recurrent disease, and to identify metachronous lesions. In case of "positive" WL and/or NBI findings, patients were scheduled for an excisional biopsy under either local or general anaesthesia. In this setting, patients underwent further intraoperative HDTV WL and HDTV NBI endoscopy.

The recorded videos of all evaluations were separately examined by 3 of the authors (G.P., C.P., and D.C.) who rated them as "positive" or "negative". The examination was considered as "positive" when at least 2 of 3 authors concurred. The sensitivity and positive predictive value of HDTV WL and HDTV NBI for the entire cohort were calculated in relation to the definitive histopathologic report. Specificity, negative predictive value, and accuracy were calculated on the basis of results obtained in a subgroup of 16 patients submitted to multiple endoscopic evaluations during follow-up. This method was chosen to overcome the drawback that "negative" areas were obviously not submitted to histopathologic examination. In fact, random biopsies of otherwise normal mucosal sites would be practically unfeasible and ethically inappropriate.

Results

Group A included 35 patients, 23 (66%) affected by OSCC and 12 (44%) with OPSCC. Fourteen of 35 (40%) patients in this group showed adjunctive endoscopic findings with HDTV NBI, undetectable by routine (non-HDTV) WL endoscopy. Only seven of these 14 patients (50%) also had adjunctive findings during HDTV WL endoscopy. All findings judged as "positive" by HDTV NBI were histologically confirmed as mild-moderate dysplasia ($n = 5$), carcinoma in situ ($n = 3$), and microinvasive carcinoma ($n = 6$). From a practical point of view, the application of HDTV NBI in this group led to an upstaging of the superficial tumour extension with

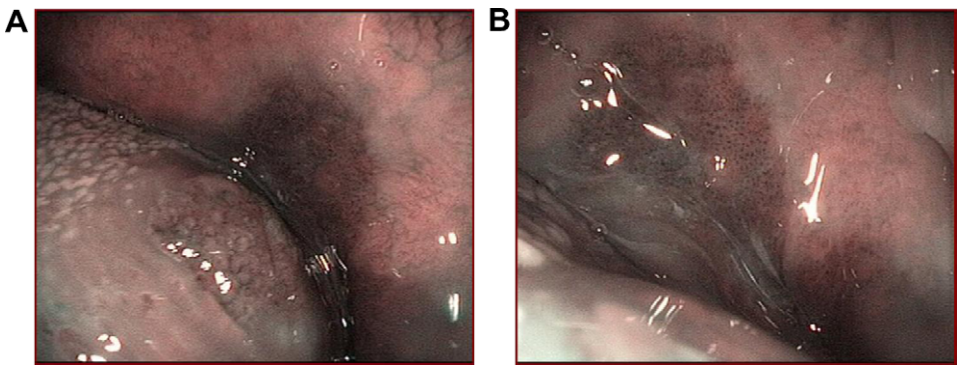

Figure 1 (A) Examination by HDTV NBI with 0° rigid telescope, showing a well-demarcated dark area in the left anterior tonsillar pillar extending to the adjacent base of tongue; and (B) closer view of the same lesion with better visualization of the typical thick brown spots expression of the neoangiogenic process.

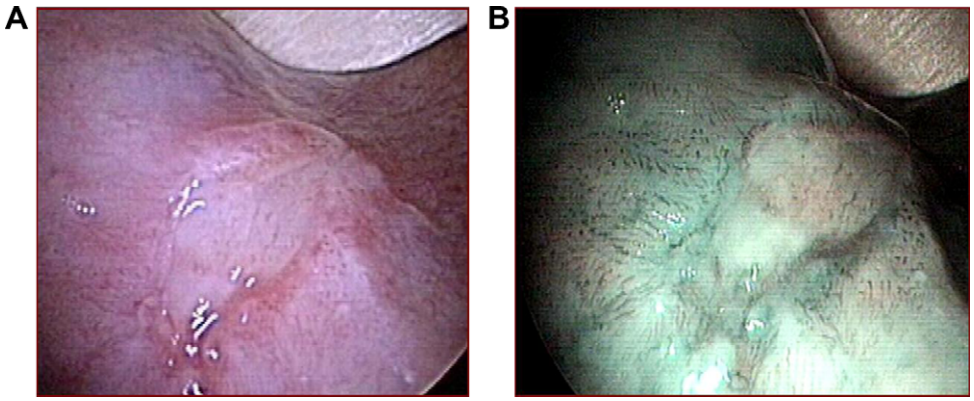

Figure 2 (A) Examination by HDTV WL with 0° rigid telescope during follow-up, in a patient previously treated by RT for OPSCC, showing a non-healing ulcer in the right floor of the mouth; and (B) same picture by HDTV NBI better defining the margins of the lesion due to the typical vascular pattern in the surrounding mucosa. This lesion was confirmed by histology to be a metachronous microinvasive OSCC.

consequent planning of a wider surgical resection ($n = 9$) (Fig. 2A and B), detection of synchronous lesions ($n = 4$), and identification of an unknown primary after fine needle aspiration cytology of a lymph node metastasis from SCC ($n = 1$).

Group B included 61 patients, 43 (70%) previously treated for OSCC and 18 (30%) for OPSCC. HDTV NBI endoscopy showed "positive" areas in 12 (20%) cases. None of the "positive" areas was visible using routine WL endoscopy, whilst HDTV WL was "positive" in only 6 (50%) cases. All the "positive" lesions by HDTV NBI were histologically confirmed as carcinoma in situ ($n = 5$), microinvasive ($n = 4$), and invasive carcinoma ($n = 3$). Therefore, HDTV NBI also played a relevant role during follow-up with early detection of incomplete tumour response to RT ($n = 1$), recurrences ($n = 6$), and metachronous tumours ($n = 5$).

If the entire cohort is taken into account, 26 of 96 patients (27%) had a diagnostic benefit by using NBI and HDTV technologies.

In the present series, all "positive" lesions at HDTV NBI ($n = 26$) were found to be true positives, and no false positive was detected. Patients were considered as true negatives when they were persistently negative at subsequent HDTV NBI evaluations with a minimum interval of 6 months. In this way, we found one false negative case in a male patient previously considered without "positive" areas at HDTV NBI, who turned out to be NBI "positive" 8 months later with a diagnosis of carcinoma in situ of the anterior tonsillar pillar.

The sensitivity, specificity, positive, negative predictive values, and accuracy of HDTV WL and HDTV NBI examinations are summarized in Table 1.

Discussion

OSCC and OPSCC still remain diseases with a potentially dismal prognosis and considerable social burden. Poor outcomes are due to the advanced stage at diagnosis, with over 60% of lesions in Stage III and IV,[10] and to the high incidence of upper aerodigestive tract second primaries, reported in 17–30% of patients, according to the "field cancerization" phenomenon.[3,11]

Table 1
Sensitivity and positive predictive values of HDTV WL and HDTV NBI for the entire cohort of patients ($n = 96$). Specificity, negative predictive value, and accuracy were calculated taking into account only patients submitted to multiple endoscopic evaluations ($n = 16$).

	HDTV WL (%)	HDTV NBI (%)
Sensitivity	51	96
Positive predictive value	100	100
Specificity	100	100
Negative predictive value	87	93
Accuracy	68	97

To improve the diagnosis of OSCC and OPSCC, several different screening methods have been developed in the last two decades. Vital tissue staining such as toluidine blue has been used for more than 40 years to aid detection of mucosal abnormalities of the larynx and oral cavity, with a median sensitivity, specificity, positive, and negative predictive values of 85%, 67%, 85%, and 83%, respectively.[4] Even though promising results have been reported, several authors found a high rate of false positive stains during oral and oropharyngeal examination, and concluded that this, together with the low specificity in staining dysplasia (50%), likely outweighs the potential benefits.[12–14]

Recently, light-based detection systems such as chemiluminescence and autofluorescence, have been adapted for evaluation of the oral and oropharyngeal cavities. By chemiluminescence, after application of acetic acid under blue-white illumination, normal epithelium appears lightly bluish, whilst abnormal epithelium appears distinctly white. Several authors reported a high sensitivity but extremely low specificity, and concluded that, at present, chemiluminescence is unable to discriminate between keratotic, inflammatory, and malignant lesions.[15–17]

By contrast, several studies have demonstrated that autofluorescence is capable of identifying lesions that cannot be seen using conventional light. Jayanthi and coworkers found that this method, based on the presence of cellular alterations with decreased levels of normal autofluorescence, is able to discriminate normal mucosa from SCC with a sensitivity, specificity, and accuracy of 86%, 90%, and 88%, respectively.[18] Nevertheless, the authors affirm that sites such as the vermilion border, lip, dorsal, and lateral sides of the tongue usually show high porphyrin-bacteria emission, with consequent false positive findings.

The application of NBI in many different anatomic sites has already demonstrated its value in detecting early lesions that are otherwise unidentifiable by standard WL endoscopy.[19–22] More recently, the technique has shown efficacy in improving the screening for and surveillance of lesions in the head and neck allowing a "virtual *in vivo* histology" and potentially eliminating the need for random biopsies.[5–9]

Watanabe et al.[7] prospectively evaluated 667 patients affected by oesophageal cancer using an NBI videoendoscope and identified an increased number of patients with head and neck cancer compared to conventional WL endoscopy (44 versus 23 lesions, respectively), with a significant difference between the sensitivity, negative predictive value, and accuracy of the two methods (97.7%, 99.8%, and 98.8%, respectively, for NBI and 51.1%, 96.6%, and 96.4%, respectively, for WL).

In a previous study, we confirmed these results by utilizing HDTV NBI in the assessment of laryngeal cancer during pre-, intra-, and postoperative endoscopic evaluation, showing a relevant diagnostic advantage in terms of better definition of surgical margins, tumour staging, and early detection of persistences, recurrences, and metachronous lesions compared to conventional endoscopy.[9]

In the present analysis, we further confirm the utility of this new technology in pre- and intraoperative settings, with better definition of superficial extension of the lesion, detection of synchronous tumours, and identification of unknown primaries. Moreover, HDTV NBI also played a relevant role during follow-up with early detection of persistences, recurrences, and metachronous tumours.

Although most authors have reported low rates of false positives by NBI (7–14%), mainly related to acute inflammation and chronic post-RT changes,[7,23] we strongly believe that the learning curve of the examiner is the most crucial factor influencing outcome. Indeed, in our experience there was no statistically significant difference between the NBI false positive rate after RT or chemo-RT compared to that of a cohort of untreated patients. In contrast, the major factor influencing the rate of false positives by NBI was related to the period of practice, being highest in the first 6 months and zero in the last six (unpublished data).

However, a potential limitation of NBI concerns estimation of its genuine specificity. Indeed, it would be ethically and practically unfeasible to perform random biopsies in every patient whom is "negative" by NBI. Watanabe et al. were the first to establish a clinically acceptable protocol for calculating the specificity of NBI. In their series, all patients judged NBI "negative" who did not develop SCC during a mean follow-up of 13 months were considered as true negatives, even though histologic confirmation was not obtained.[7] In our series, we judged true negatives only those patients who underwent more than one endoscopic NBI evaluation during follow-up and who were persistently negative. As already demonstrated by our experience in laryngeal cancer, the specificity obtained by NBI-HDTV still showed that this technology is significantly accurate in recognizing true positives and in distinguishing, at the same time, true negative patients in oral and oropharyngeal mucosal sites.

In conclusion, NBI and HDTV technologies appear to be promising diagnostic tools in the evaluation of OSCC and OPSCC. Future refinements should be achieved by enhancing these methods with oral cytology after brushing of suspected lesions and using liquid-based analysis to accurately calculate the specificity and negative predictive value of the technique, whilst avoiding unnecessary excisional biopsy of non-malignant lesions. In this light, the diagnostic potential of NBI and HDTV in defining the true nature of oral and oropharyngeal leuko-erythroplakias that have not been previously biopsied could be elucidated.

Conflicts of interest statement

None declared.

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