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Narrow Band Imaging Endoscopy of the Nasopharynx for Malignancy: An Inter- and Intraobserver Study

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Objective: To assess interobserver agreement and intraobserver reproducibility when assessing the nasopharynx for malignancy under white light and narrow band imaging endoscopy because the decision to biopsy hinges on the examiner’s perceived chance of malignancy.

Methods: An interobserver and intraobserver agreement study utilizing white light and narrow band endoscopic images of the nasopharynx. The setting was an academic referral hospital. Participants were 156 adults with suspected nasopharyngeal carcinoma who underwent white light and narrow band imaging endoscopy and biopsy. Images of the nasopharynges were subsequently scored for malignancy by four otolaryngologists. The nasopharynx was scored on 4-point scales under white light and narrow band imaging endoscopy for the likelihood of malignancy or abnormality, respectively.

Results: Intraclass correlation coefficients for interobserver agreement for nasopharyngeal malignancy for four observers under white light were 0.86, 0.89, 0.79 and 0.88 (mean 0.855), respectively; and under narrow band imaging they were 0.64, 0.68, 0.64, and 0.66 (mean 0.655), respectively (all P values < 0.001). The coefficient for interobserver reliability under white light was 0.79 (95% confidence interval [CI] 0.76–0.82; P < 0.001), which indicated strong agreement. The coefficient for interobserver reliability under narrow band imaging was 0.56 (95% CI 0.50–0.61; P < 0.001), which indicated moderate agreement.

Conclusions: Intraobserver and interobserver agreement for nasopharyngeal malignancy was strong on white light endoscopy but only moderate on narrow band imaging endoscopy. Agreement may be improved by adopting a standard set of assessment guidelines, including an objective detailed morphological analysis under white light and vasculature analysis under narrow band imaging.

Key Words: Nasopharyngeal carcinoma, narrow band imaging, endoscopy, observer variation.

Level of Evidence: 2a

INTRODUCTION

The flexible fibroscope, which is a safe instrument used by ear, nose, and throat (ENT) surgeons as a diagnostic tool in the office, is often used as a screening tool for nasopharyngeal carcinoma (NPC).

Endoscopic visualization of the nasopharynx is the ultimate step in the diagnostic workup of suspected NPC. If the appearance of the nasopharynx is suspicious for malignancy, endoscopy will aid in directing the site of biopsy. The diagnosis of NPC is made histologically on an endoscopically guided biopsy of the nasopharynx.

Because an endoscopic guided biopsy of the nasopharynx can be uncomfortable due to the additional introduction of biopsy forceps into the nasopharynx, and may bleed persistently, which requires bipolar cauterization, nasopharyngeal packing, or even hospitalization, unnecessary nasopharyngeal biopsies should be avoided unless definitely indicated.

The development of noninvasive methods for evaluation of neoplastic changes in nasopharyngeal mucosa has the potential to improve the quality of life and survival rate when malignancy is diagnosed at a superficial stage. In this regard, the introduction of narrow band imaging (NBI, Olympus Medical System Corporation, Tokyo, Japan) has shown potential to identify carcinomas at an early stage in head and neck mucosal sites.

Because a nasopharynx deemed to be normal on white light endoscopy may harbor occult NPC, there may well be a role for NBI endoscopy to assess the nasopharyngeal vasculature for abnormalities, which may indicate subclinical mucosal dysplasia or even malignancy, as is the case for the esophagus.

The aim of this article is to assess the reliability of the assessment of the degree of abnormality of the vasculature of the nasopharynx under NBI, using white light endoscopy and biopsy as standards, with an interobserver and intraobserver variability study. High interobserver reliability would indicate its reproducibility and hence
Fig. 1. A nasopharynx graded as “normal” under narrow band imaging (right image) showing normal, pale regular polygonal follicles outlined by thin darker reticular borders. The left image is the same nasopharynx under white light showing a normal nasopharynx that is smooth and symmetrical with regular polygonal follicles seen in the mucosa.8 Used with permission. Reprinted by permission from Springer Nature: European Archives of Oto-Rhino-Laryngology. Narrow band imaging endoscopy of the nasopharynx is not more useful than white light endoscopy for suspected nasopharyngeal carcinoma. Vlantis AC, Woo JKS, Tong MCF, King AD, Goggins W, van Hasselt CA. 2016.

Fig. 2. A nasopharynx graded as “enlarged vessels only” under narrow band imaging (right image) showing a multitude of abnormal enlarged vessels in the overlying mucosa. The left image is the same nasopharynx under white light showing a submucosal mass with enlarged vessels in the overlying mucosa.8 Used with permission. Reprinted by permission from Springer Nature: European Archives of Oto-Rhino-Laryngology. Narrow band imaging endoscopy of the nasopharynx is not more useful than white light endoscopy for suspected nasopharyngeal carcinoma. Vlantis AC, Woo JKS, Tong MCF, King AD, Goggins W, van Hasselt CA. 2016.

Fig. 3. A nasopharynx graded as “vascular tufts only” under narrow band imaging (right image) showing discrete tufts of vessels uniformly spread throughout the mucosa. The left image is the same nasopharynx under white light showing a submucosal mass covered by an unremarkable mucosa.8 Used with permission. Reprinted by permission from Springer Nature: European Archives of Oto-Rhino-Laryngology. Narrow band imaging endoscopy of the nasopharynx is not more useful than white light endoscopy for suspected nasopharyngeal carcinoma. Vlantis AC, Woo JKS, Tong MCF, King AD, Goggins W, van Hasselt CA. 2016.

place as an additional screening tool in the diagnostic armamentarium of the ENT surgeon.

MATERIALS AND METHODS

Approval for the study, which was performed according to the Declaration of Helsinki, was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, and informed written consent was obtained from each patient.

King et al.6 compared the accuracy of magnetic resonance imaging with that of the clinical standard of white light endoscopy and endoscopic biopsy in a prospective study of 246 patients suspected of having NPC based on a serologic screening test for NPC or on having symptoms of NPC. Patients for that study were recruited from the ENT outpatient clinic at a referral hospital in a region where NPC is endemic between January 2007 and January 2010. In that study by King et al.,6 the first author of this study (A.C.V.) performed the endoscopies on 156 patients recruited from January 2008 until the end of the study, digitally recording both white light and NBI endoscopy for subsequent re-evaluation prior to biopsy.

Endoscopy was performed under topical decongestion and anesthesia. When excessive secretions limited the ability to adequately assess the nasopharyngeal mucosa and vasculature, these were carefully aspirated under endoscopic guidance without making contact with the mucosa.

The system used for endoscopy (Visera OTV-S7 PRO; Olympus Medical Systems Corp., Tokyo, Japan) was equipped with a light source (CLV-S40 PRO; Olympus Medical Systems Corp.) and a flexible high-definition video rhinolaryngoscope (ENF-VQ; Olympus Medical Systems Corp.). The switch from the conventional white light mode to the NBI mode was achieved by an assistant pressing a button on the light source or by the endoscopist pressing a button on the endoscope. White balance was performed prior to each endoscopy. All patients then underwent a nasopharyngeal biopsy to establish the definitive diagnosis under topical anesthesia. Any abnormal or suspicious mucosa was biopsied; otherwise, the left and right posterior walls adjacent to the pharyngeal recess, a common site for NPC, were biopsied.

The archived digital videos of 156 consecutive patients were retrieved and reviewed, and representative endoscopic images of the left and right nasopharyngeals under white light and NBI were captured. Each of the 624 images was assigned a unique study number.

Four experienced otolaryngologists who were blinded to the diagnosis of the image (benign vs. NPC) viewed the images on two separate occasions at least 3 days apart. They were asked to score the nasopharynx on white light endoscopy as a) normal with or without lymphoid tissue (or adenoids), b) having a low index of suspicion for NPC, c) having a high index of suspicion for NPC, or d) having definite NPC.

As any well-demarcated brownish area with thick dark spots and/or winding vessels are considered abnormal on NBI,¹³

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they were asked to score the vasculature of the nasopharynx on NBI endoscopy as i) normal, ii) the presence of enlarged vessels only, iii) the presence of vascular tufts only, or iv) the presence of both enlarged vessels and vascular tufts. Figures 1 through 4 are corresponding examples of i to iv shown to the four otolaryngologists as examples.

Because each image was observed twice and thus was scored twice, the two values scored by each observer for each image were averaged. For the analysis under white light, normal or low index of suspicion versus high index of suspicion or definitely malignant were used. For the analysis under NBI, normal or enlarged vessels versus vascular tufts or both enlarged vessels and vascular tufts was used, as well as normal versus enlarged vessels or vascular tufts or both enlarged vessels and vascular tufts.

The intraclass correlation coefficient was used to assess the consistency, or conformity, of measurements made by the four observers measuring the same quantity. In this study the intraobserver and interobserver reliability were calculated with the intraclass correlation coefficient using single measures.

### RESULTS

Ninety men and 66 women with a mean age of 49.5 years (range, 17–85 years) were enrolled into the study. Forty-one patients had NPC confirmed on biopsy.

No complications occurred in any patient as a result of either the endoscopy or the endoscopically directed biopsy; no mucosa required diathermy; no nasal or nasopharyngeal packing was needed; and no patient was admitted to hospital for uncontrolled bleeding.

The intraclass correlation coefficients for intraobserver agreement regarding the likelihood of malignancy on white light endoscopy for each of the four observers was 0.86, 0.89, 0.79, and 0.88, respectively (mean 0.855) (all $P$ values < 0.001). The intraclass correlation coefficients for intraobserver agreement regarding the likelihood of malignancy on NBI endoscopy for each of the four observers was 0.64, 0.68, 0.64, and 0.66, respectively (mean 0.655) (all $P$ values < 0.001) (Table I).

The intraclass correlation coefficient for interobserver reliability on white light endoscopy was 0.79 (95% CI 0.76–0.82; $P < 0.001$), which indicated a strong agreement between raters for the chance of malignancy.

The intraclass correlation coefficient for interobserver reliability on NBI endoscopy was 0.56 (95% CI 0.50–0.61; $P < 0.001$), which indicated only a moderate agreement between raters for the change of malignancy.

On white light endoscopy, when a rating of either a normal or low index of suspicion was compared to a high index of suspicion or definitely malignant, the sensitivity was 86.6%; the specificity was 87.0%; the PPV was 70.3%; and the NPV was 94.8%. The values are the modes of all four observers.

On NBI endoscopy, when a rating of either a normal or enlarged vessels only was compared to vascular tufts only or vascular tufts and enlarged vessels, the sensitivity was 73.2%; the specificity was 77.0%; the PPV was 53.1%; and the NPV was 88.9%. The values are the modes of all four observers. When a rating of normal was compared to any vascular abnormality being present (enlarged vessels only or vascular tufts only or vascular tufts and enlarged vessels), the sensitivity was 92.7%; the specificity was

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**TABLE I.**

<table>
<thead>
<tr>
<th>Observer and Endoscopy Modality</th>
<th>Finding Number (%)</th>
<th>Intraclass Correlation Coefficient, Single Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Normal</strong></td>
<td><strong>Low Index</strong></td>
</tr>
<tr>
<td>Observer 1 WL</td>
<td>155 (49.7)</td>
<td>61 (19.6)</td>
</tr>
<tr>
<td>Observer 1 NBI</td>
<td>124 (39.7)</td>
<td>74 (23.7)</td>
</tr>
<tr>
<td>Observer 2 WL</td>
<td>182 (58.3)</td>
<td>43 (13.8)</td>
</tr>
<tr>
<td>Observer 2 NBI</td>
<td>185 (59.3)</td>
<td>43 (13.8)</td>
</tr>
<tr>
<td>Observer 3 WL</td>
<td>69 (22.1)</td>
<td>99 (31.7)</td>
</tr>
<tr>
<td>Observer 3 NBI</td>
<td>72 (23.1)</td>
<td>40 (12.8)</td>
</tr>
<tr>
<td>Observer 4 WL</td>
<td>133 (42.6)</td>
<td>70 (22.4)</td>
</tr>
<tr>
<td>Observer 4 NBI</td>
<td>158 (50.6)</td>
<td>82 (26.3)</td>
</tr>
</tbody>
</table>

*ICC = intraclass correlation coefficient; NBI = narrow band imaging endoscopy; NPC = nasopharyngeal carcinoma; WL = white light endoscopy.*
TABLE II. Sensitivity, Specificity and Accuracy of White Light and Narrow Band Imaging Endoscopy for the Detection of Nasopharyngeal Malignancy

<table>
<thead>
<tr>
<th>Modality</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
<th>% PPV (95% CI)</th>
<th>% NPV (95% CI)</th>
<th>% Accuracy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WL</td>
<td>86.6 (76.8%–92.8%)</td>
<td>87.0 (81.7%–90.9%)</td>
<td>70.3 (60.3%–78.8%)</td>
<td>94.8 (90.6%–97.2%)</td>
<td>86.9 (82.8%–90.9%)</td>
</tr>
<tr>
<td>NBI for (ii) or (iv)</td>
<td>73.2 (62.1%–82.1%)</td>
<td>77.0 (70.9%–82.1%)</td>
<td>53.1 (43.5%–62.5%)</td>
<td>88.9 (83.5%–92.8%)</td>
<td>76.0 (70.1%–81.4%)</td>
</tr>
<tr>
<td>NBI for (ii) or (iii)</td>
<td>92.7 (84.2%–97.0%)</td>
<td>52.6 (46.0%–59.2%)</td>
<td>41.1 (34.0%–48.6%)</td>
<td>95.3 (89.6%–98.1%)</td>
<td>63.1 (56.4%–69.9%)</td>
</tr>
</tbody>
</table>

Values are modes for all four observers. CI = confidence interval; NBI = narrow band imaging endoscopy; (ii) = enlarged vessels; (iii) = vascular tufts only; (iv) = both enlarged vessels and vascular tufts; NPV = negative predictive value; PPV = positive predictive value; WL = white light endoscopy graded as a high index of suspicion for nasopharyngeal carcinoma.

DISCUSSION

Whereas the early detection of esophageal malignancy is often difficult because many superficial carcinomas are isochromatic when examined under white light, NBI has become the method of choice for screening the esophagus for squamous cell carcinoma. This study was undertaken to determine whether NBI can reliably and reproducibly be used to screen the nasopharynx for subclinical or early-stage carcinoma when treatment would offer the best survival.

NBI is a technology that uses optical filters to select out blue and green light with wavelengths of 415 and 540 nm, respectively. These wavelengths penetrate the tissues to different depths and are strongly absorbed by hemoglobin, which enhances the contrast between vessels and tissues and enables the visualization of superficial capillaries and subepithelial veins. Under narrow-band illumination, capillaries in the mucosal layer appear brown in color, and the veins in the submucosa are green on the monitor.

The application of NBI in many different anatomic sites has already demonstrated its value in detecting early lesions that are otherwise unidentifiable by standard white light endoscopy.9–12

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.2–5,12 In addition, the appearance of the superficial microvessels in the nasopharynx of patients with NPC seen on NBI endoscopy may be associated with the radiosensitivity of the carcinoma.13

Terminology

Consensus on the detailed diagnostic criteria of NBI is needed because it is not unified or adequate at the moment.14 This was highlighted by Sun et al. in their very recent systematic review and meta-analysis of the diagnostic performance of NBI for NPC published in April 2018.15 To address this, we searched the Medline and Embase databases up to May 2018 for “(narrow band imaging) AND (nasopharynx OR nasopharyngeal)” and “NBI AND NPC.” All relevant articles published in the English literature have been cited in this article.

The appearance of abnormal vessels of the nasopharynx under NBI has been variously divided into four or five types.17–19 Wen et al. described four types: type I are short, thin, and sparse, and are located in the space among the lymphoid follicles; type II are moderate in length and diameter and reticulate regularly; type III are dilated, elongated, mildly irregular, and bifurcate; and type IV are distorted in an earthworm-like appearance, with a very irregular diameter and vessel course. Ni et al. described five types of intraepithelial papillary capillary loop patterns of nasopharyngeal microvessels detected by NBI, adding one further type to the four described by Wen et al. above, that of scattered, small dark-brown dots in which the vessels are relatively regular but of high density.

At present, the interpretation of the vascular pattern of the nasopharynx remains as subjective as that of the morphological appearance.

For this study, we divided the appearance of nasopharyngeal vessels in three types. We described the type I of Wen et al. as normal, their type II (moderate diameter) and type III (dilated and mildly irregular) as enlarged vessels, and their type IV (distorted in an earthworm-like appearance, with a very irregular diameter and vessel course) as vascular tufts. This term is widely used in the ophthalmologic literature and denotes clusters of convoluted fine vascular loops that effectively describe our findings. A tuft can be defined as a cluster of elongated strands growing close together as a dense clump. Enlarged vessels are usually not seen in the normal mucosa of the nasopharynx, and the presence of enlarged vessels of whatever caliber and tortuosity is abnormal. The presence of both enlarged vessels and vascular tufts formed our fourth category for the purposes of this analysis.

The heterogeneity of terminology used in the literature to describe normal and abnormal features of the nasopharynx on NBI should be standardized through a common consensus to aid collective reporting, understanding of the terms of reference and research. Yang et al.11 judged well-demarcated brownish areas with scattered brown spots malignant and reported that all of their squamous cell carcinoma lesions were “suspected malignant lesions” on NBI. Ho et al. noted that an irregular engorged vascular pattern and/or a
microvascular proliferative pattern was associated with NPC in 78.0% of their patients on NBI endoscopy. Wen et al.\textsuperscript{16} considered a well-demarcated brownish area or brownish spots with or without irregular type III or IV microvascular patterns to be malignant under NBI endoscopy. However, Lin et al.\textsuperscript{24} found that the prevalence rate of brownish spots in early cancer of the nasopharynx was only 11%. Whereas microvascularity can be assessed objectively, which is essential for reproducibility, the terms brownish areas or spots are perhaps open to a more subjective interpretation.

The strength of NBI endoscopy is visualization of vessels. On NBI endoscopy of the esophagus, abnormal vessels are seen in an apparently normal-looking mucosa and are the earliest detectable evidence of carcinoma. This finding has been shown to be a valuable diagnostic tool in other upper aerodigestive mucosal lesions. Similarly, our study aimed to determine if deviation from the normal vascularity of the nasopharynx seen under NBI endoscopy could be reliably repeated and reproduced by other observers.

**Comparisons With Other Studies**

Although previous studies have put the sensitivity of NBI endoscopy for malignancy at 78% to 93%, they have included features other than the vascular pattern, which is what NBI detects and assesses.\textsuperscript{16,18,20–22,25}\textsuperscript{22,25}

In 2012, Tan et al.\textsuperscript{26} reviewed the current published articles relating to NBI endoscopy for the early detection of cancer of the head and neck, and they found none concerned the nasopharynx. Oral cavity, oropharynx, hypopharynx, and larynx mucosal malignancies are usually squamous cell carcinomas unrelated to Epstein-Barr virus infection, whereas most (96% in the study by Cheung et al.\textsuperscript{27}) if not all nasopharyngeal mucosal malignancies are undifferentiated carcinomas related to EBV infection. It is possible that figures quoted in the literature for other head and neck sites may not be applicable to the nasopharynx, where the Epstein-Barr virus–related carcinoma may not invoke the same changes in mucosal vessels as occurs at other head and neck sites. This is an area that needs further study.

In our study, the sensitivity of NBI endoscopy for carcinoma was 73% when vascular tufts were present, and they had a specificity of 77.0% but a positive predictive value of only 53.1%, which is probably not clinically useful. If any abnormal vessel was used as the criterion for malignancy, then although the sensitivity of that finding was 92.7%, the specificity dropped to 52.6% and the positive predictive value to only 41.1%. In our study, abnormal vessels detected on NBI endoscopy did not achieve the same degree of accuracy or sensitivity as that of routine white light endoscopic examinations of the nasopharynx for detecting possible malignancy.

Further, although the agreement between doctors for white light endoscopy was strong (intraclass correlation = 0.79, 95% CI 0.76–0.82), it was only moderate for NBI endoscopy (intraclass correlation = 0.56, 95% CI 0.50–0.61). This may indicate the familiarity that ENT endoscopists have in assessing the nasopharynx, whereas assessing the vasculature under NBI is novel and may involve a learning curve or may indicate that abnormal vessels are detectable in the nasopharynx secondary to pathology and conditions other than malignancy of the mucosa.

**Strengths of the Study**

One strength of our study is that one or more biopsies were obtained from each nasopharynx, including those that were normal on white light and NBI endoscopy. The indications for the biopsy in the original study were not the endoscopic findings but the result of the screening serology, when eight (10%) of 77 patients with NPC were missed by endoscopy, and four (5%) of 77 patients with NPC were missed by endoscopy and biopsy.\textsuperscript{8} Thus true negatives were determined and a genuine specificity for this current study determined.

**Weakness of the Study**

A four-category option with which to assess the nasopharynx for possible NPC on white light or NBI endoscopy is inadequate, and a more detailed assessment of the morphology of the nasopharynx under white light and of the vasculature of the nasopharynx under NBI endoscopy is warranted and needs to be developed and assessed in a prospective study.

**CONCLUSION**

White light endoscopy of the nasopharynx is routine; thus, intraobserver and interobserver agreement for nasopharyngeal malignancy predictably was strong and reliable. Narrow band imaging endoscopy of the nasopharynx is novel and unusual, as evidenced by only moderate intraobserver and interobserver agreement for vessel abnormality (as a surrogate for subclinical epithelial disease). Improving intraobserver and interobserver agreement on what constitutes possible nasopharyngeal carcinoma on white light endoscopy, and especially on narrow band imaging endoscopy, is warranted. This may be achieved by formulating and adopting a standard set of assessment guidelines of the nasopharynx, including an objective detailed morphological analysis under white light and vasculature analysis under narrow band imaging endoscopy.

**BIBLIOGRAPHY**


