

High specificity of combined narrow band imaging and autofluorescence mucosal assessment of patients with head and neck cancer

Phan Nguyen,¹ Farzad Bashirzadeh, MBBS, FRACP,¹ Robert Hodge, MBBS FRACS (OHNS),² Julie Agnew, MBBS FRACS (OHNS),² Camile S. Farah, BDS, MSc, PhD, GCEd(HE), FRACDS (Oral Med) FIAAO FICD, FPFA,³ Edwina Duhig, MBBS, FRCPA,⁴ Belinda Clarke, MBBS, FRCPA, PhD,⁴ Joanna Perry-Keene, MBBS, FRCPA,⁵ David Botros, MBBS,⁵ Ian Brent Masters, MBBS, FRACP, PhD,⁶ David Fielding, MBBS, FRACP, MD (Lond.)¹

¹The Department of Thoracic Medicine, The Royal Brisbane and Women's Hospital, Herston, Queensland, Australia, ²The Department of Ear Nose and Throat Surgery, The Royal Brisbane and Women's Hospital, Herston, Queensland, Australia, ³The University of Queensland, UQ Centre for Clinical Research, Herston Queensland, Australia, ⁴Pathology Queensland, The Prince Charles Hospital, Chermside, Queensland, Australia, ⁵Pathology Queensland, The Royal Brisbane and Women's Hospital, Butterfield St. Herston, Queensland, Australia, ⁶The Department of Respiratory Medicine, The Royal Children's Hospital, Herston, Queensland, Australia.

Accepted 2 February 2012

Published online 28 June 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.22999

ABSTRACT: *Background.* The purpose of this study was to evaluate combined autofluorescence (AF) and narrow band imaging (NBI) for detection of mucosal lesions additional to known primary head and neck cancers and to determine impact on management.

Methods. Patients with head and neck cancer requiring preoperative screening or posttreatment surveillance had white light (WL), AF and NBI inspection of the head and neck and bronchus. Known primary cancers were not analyzed, only additional lesions. Moderate dysplasia or worse was considered significant.

Results. In all, 73 patients were recruited. Respectively, there were 24 and 18 additional lesions in the head and neck and bronchus that had

significant histopathology. In both regions, AF and NBI were more sensitive than WL for detecting significant dysplasia with NBI demonstrating better specificity than AF ($p = .003$); 11 of 73 patients (15.1%) had additional findings detected by AF and NBI, which had an impact on management.

Conclusion. Combined AF and NBI inspection is highly specific at panendoscopy and can influence management. ©2012 Wiley Periodicals, Inc. *Head Neck* 35: 619–625, 2013

KEY WORDS: head and neck cancer, panendoscopy, autofluorescence, narrow band imaging, field carcinogenesis

INTRODUCTION

Patients with head and neck cancer are at risk of synchronous or metachronous primary tumors in the aerodigestive tract due to field cancerization.^{1,2} In many insti-

tutions, panendoscopy is performed for the detection of such lesions with diagnostic yields under white light (WL) inspection of approximately 3%.³ Autofluorescence (AF) inspection of the head and neck and bronchus is not routinely used at panendoscopy. However, studies have shown that using AF improves the detection rates of premalignant lesions in both regions^{4–8} as well as having an impact on overall management.⁹ In the bronchus AF has been shown to have high sensitivity but poor specificity, with at least a 30% false positive rate.^{10–13} AF has also been used in the head and neck region, with sensitivities of 94% to 100% being reported for the detection of dysplasia or worse,^{14–16} with evidence that AF can detect tumor extension beyond what can be seen with white light alone.¹⁷ False-positive rates are similar to those found in the bronchus. In particular, regions around the tongue and gingival plaques can exhibit abnormal fluorescence due to microbially generated porphyrins.¹⁸

Narrow band imaging (NBI) is a simple endoscopic method that uses 2 narrow bands of light, the first at 400 to 430 nm and the second at 525 to 555 nm to only minimally penetrate the superficial mucosa and enhance the early abnormal angiogenesis seen in premalignant and malignant lesions.¹⁹ NBI has been reported to improve the sensitivity, diagnostic accuracy, and negative predictive value for the detection of early head and neck squamous cell carcinomas (SCCs) compared with white light

*Corresponding author: P. Nguyen, The Department of Thoracic Medicine, The Royal Brisbane and Women's Hospital, Butterfield St., The University of Queensland, UQ Centre for Clinical Research, Herston QLD Australia 4029. E-mail: phan.nguyen@internode.on.net

Additional Supporting Information may be found in the online version of this article.

Disclosures: Olympus Medical Systems Corp., Tokyo, Japan provided a loan ENF-VQ nasendoscope for this clinical trial; this was the only available ENF-VQ nasendoscope in Australia at the time of trial commencement. Olympus Australia Pty. Ltd. provided Dr. Phan Nguyen with partial sponsorship to attend the 12th Asia Oceania ORL-HNS Congress in Auckland 2011 to present results of this clinical trial. Olympus Australia had no input in the design, patient recruitment, or analysis of results of this trial. Dr. Phan Nguyen has received a single one-off payment for a speech at Olympus Australia's training conference. This was to nonmedical staff. All medical speeches have been unfunded. There are no ongoing lecture fees.

Presentations at international meetings: This work has been presented at the following international and local meetings: The Tri-Society Head and Neck Oncology Meeting in Singapore September 2011. The 12th Asia Oceania Otolaryngology Congress in Auckland, March 2011, Oral Presentation, 14th World Conference on Lung Cancer, Amsterdam, July 2011, Poster Presentation; preliminary data were presented at the Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Brisbane 2010.

TABLE 1. Visual grading of white light, autofluorescence, and narrow band imaging findings.

Grade	White light	Autofluorescence	Narrow band imaging
1	No visual abnormality	Green image	Normal mucosal vascularity
2	Erythema, swelling/thickening of mucosa. Inflammation, fibrosis, trauma, and granulation.	Slight decrease in fluorescence with poorly defined margins. Faint violet image.	Increased capillary density and fewer than 2 criteria as outlined in grade 3.
3	Nodular, polypoid lesions; irregular mucosa.	Definite decrease in fluorescence with clearly defined margins. Violet image.	More than or equal to 2 criteria present: brown discoloration; capillary loops; dotted vessels; tortuous vessels; abrupt-ending vessels.

inspection.^{20–23} It has also been shown to be effective in detecting second primary cancers in patients with previous oral SCCs.²⁴ In the bronchus, NBI has been shown to be more specific than AF without compromising its sensitivity.²⁵ Well-characterized changes can be seen that correspond to an early increase in vascularization of lesions of severe dysplasia or worse; these include intrapapillary capillary loops (IPCLs) and tortuosity of vessels.²⁶ No prospective data are available that combine WL, AF, and NBI inspection of the head and neck and bronchus regions to compare their relative sensitivities and specificities. Nor are there data available on how the combined addition of AF and NBI can have an impact on management of patients with head and neck cancer.

We used AF and NBI in patients with head and neck cancer planned for panendoscopy as part of their diagnostic workup. The aim was to screen for additional lesions to the primary head and neck cancer, both in the upper aerodigestive tract and in the bronchus, and to determine how these had an impact on overall management. Furthermore, we wanted to determine if the addition of NBI improved the poor specificity of AF without influencing overall sensitivity.

MATERIALS AND METHODS

The study was performed at The Royal Brisbane and Women's Hospital, Queensland, Australia, and was approved by the Human Research Ethics Committee of this institution (08/QRBW/20). Patients were prospectively recruited from the hospital's large multidisciplinary head and neck cancer clinic. Consecutive patients with known SCC of the head and neck, and patients with SCC of unknown primary origin, planned for panendoscopy as part of their diagnostic workup were enrolled. In addition, patients were enrolled who had previously completed definitive treatment for head and neck SCC, but required reassessment with panendoscopy because of suspicion of recurrent disease. Informed consent was obtained in all cases. Patients with poor functional status or with cancers planned for palliative management only were excluded.

The Wolf autofluorescence system was used (Diagnostic Autofluorescence Endoscopy [DAFE]; Richard Wolf, Knittlingen, Germany); Combilight PN 5138 light source and processor, and ICCD Endocam PN 5520 camera. The NBI bronchoscopic system used consisted of the Olympus NBI ENF-VQ nasendoscope for inspection of the oral cavity and larynx/hypopharynx; the Olympus

T180 bronchoscope for inspection of the tracheobronchial tree; and the CLV-180 light source and processor, which has the NBI filter (Olympus Medical Systems Corp., Tokyo, Japan). Both the AF and NBI equipment used in this study are of standard definition format.

The procedures were undertaken in the bronchoscopy suite prior to the panendoscopy. White light inspection occurred first. AF and NBI inspection of the upper aerodigestive tract was performed by a single physician (P.N.) who scored suspicious lesions in accord with the criteria outlined in the following text. This physician was aware of each patient's clinical history. It was important to have a single physician perform this part of the procedure to enable an accurate report of findings in this region to the multidisciplinary clinic to ensure correct sites for additional biopsies at the subsequent panendoscopy, and to allow management decisions to be made. Still images of biopsied lesions were captured at the shortest possible focal length in Windows Live Movie Maker (freeware; 2010 Microsoft Corporation). A second physician scored these AF and NBI images of biopsied sites. This physician was blinded to results of histopathology of the lesions. This was done to provide a second independent visual score of AF and NBI findings in the head and neck region.

Standard preoperative panendoscopy was done by ear nose throat (ENT) surgeons, which included white light esophagoscopy; AF and NBI inspections of the esophagus were not done because we did not have AF equipment for this region. Random biopsies of sites deemed normal by AF and NBI were performed by the ENT surgeons in accord with usual practice.

In the bronchus, AF and NBI inspections were performed by 2 different thoracic physicians experienced with these 2 technologies. Each was blinded to the results of the other bronchoscopy. Sites for biopsy were recorded independently during each procedure and biopsies taken after both had been completed. Random biopsies were not taken since others have shown a very low false negative rate for these 2 techniques.²⁵ Optical findings were reported in accord with the grading system outlined in Table 1, which was adapted from previously established criteria.^{25,27}

Any lesion not normal by any imaging modality (grade 2 or worse) was biopsied. Biopsies of the head and neck region were performed by ENT surgeons at the time of panendoscopy with the aid of digital photos and video recordings of the abnormal areas. Biopsies of the

bronchus were performed at the time of AF and NBI bronchoscopy.

Statistical analysis

For statistical purposes, lesions graded as 3 on the visual scale were considered significant, and biopsies of moderate dysplasia or worse in accord with the World Health Organization grading system for SCC for the head and neck and bronchus were considered pathologically significant. The known primary carcinomas were not included in the final analysis. All significant head and neck histopathology results (moderate dysplasia or worse) were confirmed by a reference head and neck pathologist. Two reference lung pathologists were used to assess all bronchial biopsies.

Results were expressed in 2 ways. First, in accord with previous authors using these 2 modalities in the bronchus,²⁵ the performances of AF and NBI were reported for lesions of moderate dysplasia or worse. Results were analyzed on a per lesion basis, with sensitivity and specificity with 95% confidence intervals (CIs) of each imaging modality reported independently. Fisher’s exact test was used to compare the relative sensitivity and specificity for white light, AF, and NBI. A 2-tailed value of *p* < .05 was taken to be significant.

Second, results were reported in terms of biopsy results, which had an immediate impact on management. Since field cancerization is well described in this patient population, AF and NBI detection of carcinoma, carcinoma in situ (CIS), and severe dysplasia lesions were considered immediately actionable by the head and neck clinic. Mild and moderate dysplasias were not considered immediately actionable.

RESULTS

Prospective patient recruitment occurred over an 18-month period between June 2009 and November 2010 inclusive. In total 73 patients were enrolled and their characteristics are summarized in Table 2. Forty-seven of the 73 patients (64.4%) had panendoscopy in the context of a newly diagnosed head and neck cancer; 10 of 73 patients (13.7%) had an SCC of unknown primary origin; and 16 of 73 patients (21.9%) were referred for reassessment because of clinical concern having previously completed definitive treatment for a head and neck cancer. Three patients did not have bronchoscopic inspection of the tracheobronchial tree because of concern regarding airway compromise due to the size of their primary carcinomas. No complications were noted for any of the AF or NBI examinations.

Of the 10 patients who had SCC of unknown primary origin, 1 of 10 patients (10%) had the primary detected by both fluoro-D-glucose positron emission tomography (FDG-PET) CT and AF/NBI inspection. Nine of 10 patients (90%) did not have the primary detected by FDG-PET-CT. Of these 9, 2 of 9 patients (22%) had the primary detected by AF and NBI with both cases being CIS in the right pyriform fossa. These cases are described in the impact on management section. The remaining 7 cases found no primary lesion after random biopsies were taken at panendoscopy.

TABLE 2. Patient characteristics and reasons for panendoscopy.

Factor	No. (%)
Sex	
Male	58/73 (79.5%)
Female	15/73 (20.5%)
Mean age, y	64.15 ± 8.23
Smoking history	5/73 (6.8%) lifelong nonsmokers
	68/73 (93.2%) current or ex smokers
	Mean 40.30 ± 15.6 pack years
Alcohol history	9/73 (12.3%) consumed more than 40 grams per day
Reasons for panendoscopy	
Primary head and neck tumor site	47/73 (64.4%)
Larynx/hypopharynx	22
Floor of mouth	10
Tonsil/soft palate	8
Tongue	4
Retromolar trigone	1
Gingiva	1
Buccal mucosa	1
SCC of unknown primary origin	10/73 (13.7%)
Referred for reassessment because of clinical concern. Previously completed definitive treatment for head and neck cancer.	16/73 (21.9%)

Abbreviation: SCC, squamous cell carcinoma.

Head and neck region

In the head and neck region there were 42 extra biopsies taken because of abnormal AF or NBI findings. Histopathology of these showed 17 normal/inflammatory lesions (40.5%), 1 mild dysplasia (2.4%), 6 moderate dysplasias (14.3%), 11 severe dysplasias (26.2%), and 7 carcinomas in situ (16.7%). Two patients had grade 3 suspicious changes detected in the larynx with AF and NBI, which were thought to be inflammatory changes only under WL. Histopathology at the initial panendoscopy for these patients both suggested fungal infection. However, both progressed rapidly clinically, and at repeat panendoscopy approximately 2 months later biopsy revealed invasive SCC in both cases. Only the original biopsy results were included in the final results.

For lesions of moderate dysplasia or worse, sensitivity of WL was 0.375 (95% CI, 0.21–0.57) and the specificity was 0.95 (95% CI, 0.75–0.99). AF and NBI had the same sensitivity: 0.96 (95% CI, 0.80–0.99). The specificity of AF was 0.26 (95% CI, 0.12–0.49), whereas for NBI it was 0.79 (95% CI, 0.57–0.91). Both AF and NBI were significantly more sensitive than WL (*p* = .003). The specificities of WL and NBI were not significantly different (*p* = .34), with both modalities being more specific than AF: *p* < .0001 and *p* = .003 compared with WL and NBI, respectively. In addition, there were 66 random biopsies that were negative for dysplasia or malignancy and also negative at the time of AF and NBI inspection.

TABLE 3. Sensitivity and specificity of white light, autofluorescence, and narrow band imaging.

	White light	Autofluorescence	Narrow band imaging
Head and neck			
True positive			
Number of moderate, severe, or CIS lesions with positive optical findings.	9/24 (37.5%)	23/24 (95.8%)	23/24 (95.8%)
Sensitivity	0.375 (95% CI, 0.21–0.57)	0.96 (95% CI, 0.80–0.99)	0.96 (95% CI, 0.80–0.99)
True negative			
Number of normal, metaplasia or mild dysplasia lesions with negative optical findings.	18/19 (94.7%)	5/19 (26.3%)	15/19 (78.9%)
Specificity	0.95 (95% CI, 0.75–0.99)	0.26 (95% CI, 0.12–0.49)	0.79 (95% CI, 0.57–0.91)
<i>p</i> = .003			
Bronchus			
	White light	Autofluorescence	Narrow band imaging
True positive			
Number of moderate, severe, or CIS lesions with positive bronchoscopic findings.	3/18 (16.7%)	14/18 (77.8%)	16/18 (88.9%)
Sensitivity	0.17 (95% CI, 0.06–0.39)	0.78 (95% CI, 0.55–0.91)	0.89 (95% CI, 0.67–0.97)
True negative			
Number of normal, metaplasia or mild dysplasia lesions with negative bronchoscopic findings.	44/46 (95.7%)	25/46 (54.3%)	39/46 (84.8%)
Specificity	0.96 (95% CI, 0.85–0.99)	0.54 (95% CI, 0.40–0.68)	0.85 (95% CI, 0.72–0.92)
<i>p</i> = .003			

Abbreviations: CIS, carcinoma in situ; CI, confidence interval.

On blinded review of still images by the second physician of biopsied lesions in the head and neck region only 2 NBI images were reported differently. One was a fungal lesion correctly scored as a 2; this lesion was incorrectly scored as a 3 by the first investigator. The other was a CIS lesion incorrectly scored as a 2; this lesion was correctly scored as a 3 by the first investigator. These 2 discrepancies in visual scores resulted in no difference in specificity findings between the 2 investigators.

Bronchus

In the bronchus, there were 67 extra biopsies taken because of abnormal AF or NBI. Histopathology of these showed 28 normal/inflammatory lesions (41.8%), 10 metaplasias (14.9%), 11 mild dysplasias (16.4%), 12 moderate dysplasias (17.9%), and 6 severe dysplasias (8.9%). No CIS lesions or invasive endobronchial carcinomas were found.

For lesions of moderate dysplasia or worse, white light sensitivity was 0.17 (95% CI, 0.06–0.39) and specificity was 0.96 (95% CI, 0.85–0.99). For AF, the sensitivity and specificity respectively were 0.78 (95% CI, 0.55–0.91) and 0.54 (95% CI, 0.40–0.68), and for NBI it was 0.89 (95% CI, 0.67–0.97) and 0.85 (95% CI, 0.72–0.92), respectively. Both AF and NBI were more sensitive than WL for detecting significant dysplasia ($p = .0006$ and $p < .0001$, respectively). The sensitivities of AF and NBI were not significantly different ($p = .66$); however, NBI was more specific than AF ($p = .003$). Table 3 summarizes the results for both the head and neck and bronchus regions.

Impact on management

In 11 of 73 cases (15.1%), AF and NBI inspection significantly influenced definitive management. These cases are summarized in Table 4 for carcinoma and CIS lesions

and for severe dysplasia lesions (Figures 1 and 2 are cited in Table 4). Six of the 11 cases (54.5%) found involved the larynx, 2 of 11 cases (18.2%) were unknown primary cancers with the primary detected in the right pyriform, 1 of 11 cases (9.1%) was a primary tonsillar lesion, 1 of 11 cases involved the tongue (9.1%), and 1 of 11 cases (9.1%) was a retromolar trigone SCC.

Not included in Table 4 was an additional patient who had negative AF and NBI findings at the anterior commissure, which was considered to be suspicious at white light panendoscopy. AF and NBI bronchoscopy was performed to determine if the white light findings were a true positive. We detected no involvement of the anterior commissure and laser resection proceeded instead of radiotherapy and the lesion was completely excised.

Furthermore, not included in Table 4 were an additional 3 patients who had additional findings detected by AF and NBI, which did not immediately influence definitive management but did alter long-term follow-up. Their cases are summarized in Table 5 (Figure 3 is cited in Table 5).

In the bronchus, the 12 moderate dysplasias and 6 severe dysplasias were detected in a total of 8 of 73 patients (11%). One of the 8 patients required endobronchial argon plasma coagulation for persistent severe dysplasia. The remaining 7 of 8 patients have either already had or are awaiting follow-up surveillance bronchoscopy, but none has as yet required argon plasma coagulation for persistent high-grade endobronchial dysplasia. Surveillance is important, because up to 10% of moderate dysplasias and up to 30% of severe dysplasias can progress to invasive SCC.²⁸

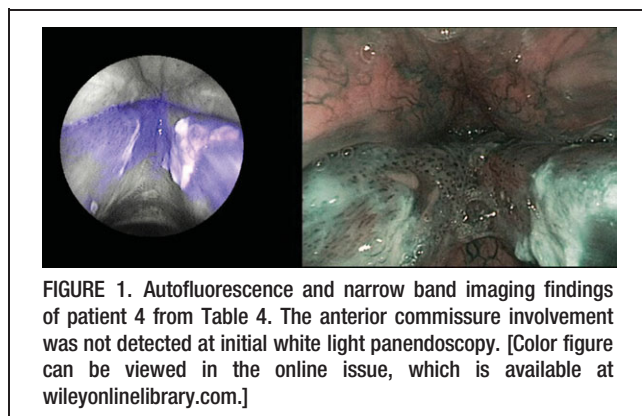
DISCUSSION

To date there have been no prospective studies that have added both AF and NBI to WL panendoscopy as

TABLE 4. Immediate management changes due to autofluorescence and narrow band imaging findings for carcinoma and CIS lesions and for severe dysplasia lesions.

Case history	Additional AF and NBI findings	Change in management
Carcinoma and CIS lesions		
Patient 1: Previous radiotherapy to right vocal cord SCC.	Detected anterior commissure SCC that extended into the subglottic region that was not detected at WL panendoscopy.	Management changed from laser resection to laryngectomy with histology, confirming tumor extension into the trachea.
Patient 2: Right vocal cord SCC. Planned for laser resection.	Detected anterior commissure SCC involvement and anterior left vocal cord involvement.	Management changed from laser resection to radiotherapy.
Patient 3: Right vocal cord SCC, suspicious epiglottis. Planned for laser resection.	Detected anterior commissure and more extensive epiglottis involvement with SCC, tracking across midline.	Extent of disease greater than first assessed under WL, and management changed to radiotherapy.
Patient 4: Right vocal cord CIS. Anterior commissure assessed as clear under WL inspection. Planned laser resection.	Anterior commissure detected to be involved. This was not seen at the initial WL panendoscopy (Figure 1).	Management changed from laser resection to radiotherapy.
Patient 5: Unknown primary.	Right pyriform CIS lesion detected.	Enabled resection of primary site.
Patient 6: Unknown primary with a right cervical chain lymph node.	Right pyriform CIS lesion detected (Figure 2, Video 1). This was not detected at WL microlaryngoscopy.	Enabled laser resection of primary site along with neck dissection and radiotherapy.
Patient 7: Previous CIS palate and right tonsil.	Detected CIS recurrence in the right tonsillar region and right posterior tongue not seen under WL.	Enabled accurate mapping of the lesion for laser resection.
Patient 8: Left retromolar trigone SCC planned for wide local excision.	Detected extension onto the tongue.	Wider resection margin taken. Histopathology showed that there was CIS (not seen under WL inspection) surrounding the primary SCC and that both were completely resected.
Severe dysplasia lesions		
Patient 9: SCC left tongue.	Detected additional severe dysplasia lesion in the left floor of mouth, which was not seen under WL.	Surgical margins widened to resect the additional floor of mouth severe dysplasia at the time of tongue resection.
Patient 10: Previous left vocal cord SCC with resection.	Detected persistent severe dysplasia of left vocal cord classified as nonsignificant leukoplakia under WL.	Repeat laser resection of vocal cord lesion.
Patient 11: WL inspection detected a lesion on the right vocal cord assessed as being benign.	Detected severe dysplasia on the right vocal cord.	Laser resection of vocal cord lesion.

Abbreviations: CIS, carcinoma in situ; SCC, squamous cell carcinoma; WL, white light; AF, autofluorescence; NBI, narrow band imaging.



part of the standard diagnostic workup for patients with head and neck cancer. We have previously reported on the addition of AF to WL inspection, which changed management in 6% of patients.⁹ In that series, despite improved sensitivity, the low specificity meant an increase in unnecessary biopsies. The data presented here address that problem with the addition of NBI. Whereas both modalities have been investigated together in the bronchus, with a similar yield for lesions of moderate dysplasia or worse as in our series,²⁵ AF and NBI have been studied independently only in the head and neck.^{22,24,26,29} Our results confirm previous findings that NBI is more specific than AF without compromising sensitivity, using a World Health Organization (WHO) grading of moderate dysplasia or worse as a marker of their

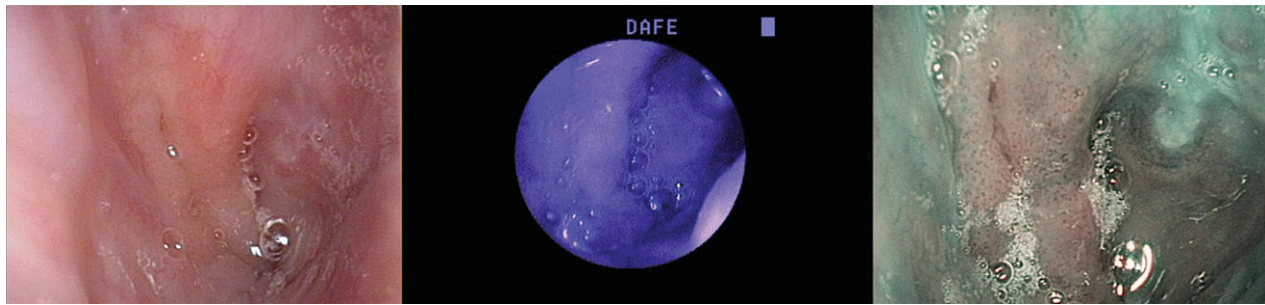


FIGURE 2. White light, autofluorescence, and narrow band imaging findings of the right pyriform sinus of patient 6 from Table 4. White light inspection failed to detect carcinoma in situ (CIS) in this region. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

relative performances in accord with previous authors.²⁵ NBI displays distinct vascular patterns in the presence of dysplasia and CIS and suffers less from the false positives of AF due to trauma, inflammation, previous biopsies, or treatment (such as diathermy or radiotherapy). Indeed the specificity of AF in our study is poorer than that in previously reported studies because a proportion of the patients had had previous definitive treatment. This caused false-positive AF findings, but also helped to highlight the benefit of having NBI available to improve the specificity of findings in patients who had undergone previous treatments or biopsies.

The head and neck samples were taken on the basis of use of AF and NBI by 1 clinician so they best indicate the utility of the combined modalities. The review of the procedural videos by another physician showed disagreement on only 2 lesions and this supports the utility of NBI alone because of its specificity. Furthermore, data from the bronchus support the possible use of NBI as an independent screening tool because 2 different proceduralists had to detect the lesions with only a single modality, demonstrating the equivalent sensitivity and superior specificity of NBI.

We found that these imaging modalities were useful in directing management plans, especially in laryngeal cases.

In particular, the flexible nature of the instruments and their magnified views allowed for easy assessment of the vocal cords and anterior commissure, which can sometimes be difficult with rigid nonmagnifying instruments. This allowed for directed biopsies at the time of panendoscopy or microlaryngoscopy. AF or NBI inspection of the head and neck region alone can easily be done in the outpatient setting with topical anesthesia in the same manner as traditional white light nasendoscopy. This adds minimal time to the usual consultation once the learning curve with these imaging techniques has been achieved.

In the bronchus, the flexible scope allows for easier access to the subsegmental bronchi not usually accessible by traditional rigid white light panendoscopy. Our study found that 8 of 74 patients (11%) had at least 1 lesion of moderate dysplasia or worse. Only 3 of 18 of these lesions (16.7%) (in 3 separate patients) were found to be abnormal under WL inspection, meaning that 15 of 18 lesions (83.3%) required AF or NBI to detect them. This group of patients is at increased risk of lung cancer, and previous authors have demonstrated the value of AF bronchoscopy for surveillance of early central airways lung cancer in this patient population with opportunity for less invasive, endobronchial treatments.⁷ However,

TABLE 5. Patients with additional AF and NBI findings that altered long-term follow-up.

Case history	Additional AF and NBI findings	Change in long-term follow-up
Patient 1: Suspicious lesion detected on left vocal cord at WL nasendoscopy.	AF and NBI inspection detected lesions at the left vocal cord, left arytenoids and left false cord (the latter 2 not seen under WL).	Histopathology confirmed moderate dysplasia in all 3 regions. Close surveillance of these 3 regions; no additional management as yet.
Patient 2: Previous left vocal cord and false cord CIS excised with LASER. Recent WL inspection deemed to be normal.	AF and NBI bronchoscopy detected an abnormal region on the left false cord (Figure 3).	Biopsy at next ear, nose, and throat surgical follow-up confirmed severe dysplasia.
Attended for follow-up bronchoscopy of endobronchial dysplasias.		Excision of these areas was performed at a later date using the images obtained at AF and NBI bronchoscopy.
Patient 3: Three previous floor of mouth carcinomas excised over period of 14 years.	AF and NBI inspection detected a suspicious lesion adjacent to a skin graft in the right floor of his mouth.	Initial biopsy confirmed moderate dysplasia and prompted close surveillance. Four months later, NBI changes were persistent, leading to excision of this lesion, which confirmed a small focus of SCC with clear margins.

Abbreviations: CIS, carcinoma in situ; SCC, squamous cell carcinoma; WL, white light; AF, autofluorescence; NBI, narrow band imaging.

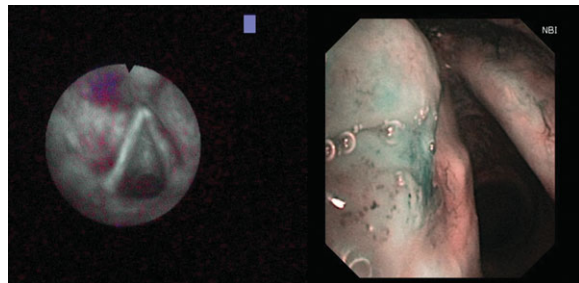


FIGURE 3. Autofluorescence and narrow band imaging of a false cord high-grade dysplasia discovered at routine follow-up bronchoscopy (patient 2 from Table 5). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the long-term impact of endobronchial dysplasia on survival in patients with head and neck cancer is unknown and requires further study, preferably in a randomized and multicenter design. Furthermore, there are the issues of added procedural time with sedative anesthetics and the need for long-term follow-up of such lesions.

In the future, high-definition and higher-magnification endoscopes and bronchoscopes will continue to improve the images obtained, perhaps allowing us to visualize abnormal vasculature adequately with WL alone. Presently though, the addition of AF and NBI to white light panendoscopy does allow the clinician to quickly detect suspicious lesions and that in our experience usually such lesions are more easily seen with AF, with NBI providing improved specificity and targeted sites for biopsy. However, we do note that, in contrast, a recent similar-sized study by Sweeny et al³⁰ found that AF was no better than WL in detecting oral cancer in patients with a previous history of head and neck cancer.

In terms of study limitations, the single-operator and nonrandomized inspection of the head and neck region meant that results for that region were combined-modality results. However, whereas sensitivity results reflect the combined-modality approach, the specificity results can still be viewed independently using histology as the final arbiter. In addition, we were able to demonstrate reproducibility of the specificity results via independent scoring of the AF and NBI images by a second investigator.

CONCLUSION

AF and NBI inspection adds to WL evaluation in patients with head and neck cancer. NBI improves specificity and can have a direct impact on patient management.

Acknowledgements

The authors thank The Cancer Council of Queensland Australia, The Australian Lung Foundation, and The Royal Brisbane and Women’s Hospital Foundation for their PhD scholarship support of Dr. Phan Nguyen.

REFERENCES

1. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953;6:963–968.
2. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. *Cancer* 1994;74:1933–1938.

3. Stoeckli SJ, Zimmermann R, Schmid S. Role of routine panendoscopy in cancer of the upper aerodigestive tract. *Otolaryngol Head Neck Surg* 2001;124:208–212.
4. Arens C, Glanz H, Dreyer T, Malzahn K. Compact endoscopy of the larynx. *Ann Otol Rhinol Laryngol* 2003;112:113–119.
5. Onizawa K, Okamura N, Saginoya H, Yoshida H. Characterization of autofluorescence in oral squamous cell carcinoma. *Oral Oncol* 2003;9:150–156.
6. Bertrand D, Righini C, Ferretti G, Brambilla C, Moro-Sibilot D. [Early diagnosis of bronchial carcinoma after head and neck cancer]. *Rev Mal Respir* 2008;25:559–568.
7. Lee P, de Bree R, Brokx HA, Leemans CR, Postmus PE, Sutedja TG. Primary lung cancer after treatment of head and neck cancer without lymph node metastasis: Is there a role for autofluorescence bronchoscopy? *Lung Cancer* 2008;62:309–315.
8. Farah C, McIntosh L, Georgiou A, McCullough M. The efficacy of autofluorescence imaging (VELScope) in the visualisation of oral mucosal lesions. *Head Neck* 2011.
9. Fielding D, Agnew J, Wright D, Hodge R. Autofluorescence improves pre-treatment mucosal assessment in head and neck cancer patients. *Otolaryngol Head Neck Surg* 2010;142 (3Suppl 1):S20–S26.
10. Hirsch FR, Prindiville SA, Miller YE, et al. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study. *J Natl Cancer Inst* 2001;93:1385–1391.
11. Lam S, Macaulay C, Leriche JC, Ikeda N, Palcic B. Early localization of bronchogenic carcinoma. *Diagn Ther Endosc* 1994;1:75–78.
12. Lam S, MacAulay C, LeRiche JC, Palcic B. Detection and localization of early lung cancer by fluorescence bronchoscopy. *Cancer* 2000;89 (Suppl 11):2468–2473.
13. Edell E, Lam S, Pass H, et al. Detection and localization of intraepithelial neoplasia and invasive carcinoma using fluorescence-reflectance bronchoscopy: an international, multicenter clinical trial. *J Thorac Oncol* 2009;4:49–54.
14. Onizawa K, Saginoya H, Furuya Y, Yoshida H, Fukuda H. Usefulness of fluorescence photography for diagnosis of oral cancer. *Int J Oral Maxillofac Surg* 1999;28:206–210.
15. Kulapaditharom B, Boonkitticharoen V. Performance characteristics of fluorescence endoscope in detection of head and neck cancers. *Ann Otol Rhinol Laryngol* 2001;110:45–52.
16. Fryen A, Glanz H, Lohmann W, Dreyer T, Bohle RM. Significance of autofluorescence for the optical demarcation of field cancerisation in the upper aerodigestive tract. *Acta Otolaryngol* 1997;117:316–319.
17. Poh CF, Zhang L, Anderson DW, et al. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. *Clin Cancer Res* 2006;12:6716–6722.
18. De Veld DC, Witjes MJ, Sterenberg HJ, Roodenburg JL. The status of in vivo autofluorescence spectroscopy and imaging for oral oncology. *Oral Oncol* 2005;41:117–131.
19. Uedo N, Ishihara R, Iishi H, et al. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006;38:819–824.
20. Muto M, Minashi K, Yano T, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010;28:1566–1572.
21. Katada C, Tanabe S, Koizumi W, et al. Narrow band imaging for detecting superficial squamous cell carcinoma of the head and neck in patients with esophageal squamous cell carcinoma. *Endoscopy* 2010;42:185–190.
22. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging for early detection of laryngeal cancer. *Eur Arch Otorhinolaryngol* 2009;266:1017–1023.
23. Tan NC, Herd MK, Brennan PA, Puxeddu R. The role of narrow band imaging in early detection of head and neck cancer. *Br J Oral Maxillofac Surg* 2012;50:132–136.
24. Chu PY, Tsai TL, Tai SK, Chang SY. Effectiveness of narrow band imaging in patients with oral squamous cell carcinoma after treatment. *Head Neck* 2012;34:155–161.
25. Herth FJ, Eberhardt R, Anantham D, Gompelmann D, Zakaria MW, Ernst A. Narrow-band imaging bronchoscopy increases the specificity of bronchoscopic early lung cancer detection. *J Thorac Oncol* 2009;4:1060–1065.
26. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging endoscope for early head and neck cancers. *Otolaryngol Head Neck Surg* 2008;138:446–451.
27. Lee P, van den Berg RM, Lam S, et al. Color fluorescence ratio for detection of bronchial dysplasia and carcinoma in situ. *Clin Cancer Res* 2009;15:4700–4705.
28. Banerjee AK. Preinvasive lesions of the bronchus. *J Thorac Oncol* 2009;4:545–551.
29. Arens C, Dreyer T, Malzahn K, Glanz H. Direct and indirect autofluorescence laryngoscopy in the diagnosis of laryngeal cancer and its precursor lesions. *Otolaryngol Pol* 2004;58:197–203.
30. Sweeny L, Dean NR, Magnuson JS, Carroll WR, Clemons L, Rosenthal EL. Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening. *Otolaryngol Head Neck Surg* 2011;145:956–960.