Role of NBI and WLE in Diagnosis of Barrett’s Esophagus in Patients with Chronic Gastroesophageal Reflux Disease

Enaase Barakat, Maha Ragab Habeeb, Neven Farouk Abass

Abstract

**Background:** Recent data have emerged that a targeted biopsy technique using Narrow-Band Imaging (NBI) could be considered in patients undergoing surveillance for Barrett’s esophagus (BE). **Aim of the study:** to determine the role of NBI compared to conventional- white light endoscopy (WLE) in diagnosis of Barrett’s esophagus in patients with chronic gastroesophageal reflux disease. **Patients and methods:** the study included 274 patients with chronic reflux symptoms, conventional-white light endoscopy (WLE) was done in all cases for diagnosis of BE. Ninety patients showed Barrett’s mucosa pattern by white-light endoscopy so 4-random biopsies were taken and examined by histopathology for detection of columnar-lined intestinal metaplasia, then patients who showed negative histopathology for intestinal metaplasia were re-endoscoped and NBI targeted biopsies were taken for histopathological confirmation of presence of intestinal metaplasia. Based on histopathology results, patients were divided into 2 groups, group 1 (BE positive, 80 patients) and group 2 (BE negative, 10 patients). Group showed increased detection rates in age > 30 years. **Results:** 90 patients had columnar-lined epithelium (CLE) by WLE (32.8%); Seventy- three patients with 4 quadrant biopsy technique confirmed to have intestinal metaplasia (81.1% of cases with endoscopic BE, and 26.6% of all screened patients), 17 patients with negative histopathology for BE were re-examined endoscopically and NBI - targeted biopsies were taken, 7 patients of them showed intestinal metaplasia, so total patients confirmed to have BE has risen to 80 patients (88.9%). **Conclusion:** NBI- targeted biopsies could diagnose BE in patients tested negative by WLE taken biopsies

**Key words:** Barrett’s, reflux, narrow band imaging, white light endoscopy.
Introduction:
Barrett’s esophagus (BE) is the only known precursor lesion to esophageal adenocarcinoma (1) which has now become the fifth leading cause of cancer-related death in men worldwide (2).

The prevalence of BE has increased in recent years, it has been detected in about 15% of patients with chronic GERD and in approximately 1–2% of population subjects (3,4). Increasing age, male gender, tobacco smoking have been proved to be risk factors for BE, moreover, obesity, positive family history, metabolic syndrome, type 2 diabetes mellitus, and sleep apnea have been identified as potential BE risk factors (5).

Endoscopic surveillances of BE has been recommended in various guidelines by different gastroenterological societies, and so, has been widely implemented. (6-11)

The gold standard diagnosis of BE is white light endoscopy (WLE) with multiple biopsies according to the Seattle protocol. This involves biopsies at 1-2 cm in a quadrantic approach. However, WLE is associated with limited sensitivities, biopsy sampling errors, significant cost, and poor adherence to the Seattle protocol, so there has been a tendency to use enhanced imaging to eliminate the need for excessive biopsies as per the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative (12).

Recent data have emerged that a targeted biopsy approach using Narrow-Band Imaging (NBI) could be considered in patients undergoing surveillance for BE (13).

Narrow band imaging (NBI) is an advanced endoscopic technique concerned in the assessment of surface patterns and microvascular architecture by utilization of a narrowed spectrum light. Blue and green wavelengths are selected by optical filters, with the elimination of red light (14). These lights with narrowed bandwidths penetrate the superficial mucosal structures and are better absorbed by hemoglobin, yielding an enhancement of mucosal features and blood vessels (capillaries from superficial mucosal layer, deeper mucosal and submucosal vessels) (15, 16).

The aim of this study is to determine the role of NBI compared to conventional white light endoscopy (WLE) in diagnosis of Barrett’s esophagus in patients with chronic gastroesophageal reflux disease.

Patients and methods:
This was a prospective study including 274 patients with chronic reflux symptoms, selected from patients attending the inpatient
and outpatient clinics of the gastroenterology and Hepatology unit at the Internal Medicine Department, Riyadh National Hospital, Saudi Arabia, between July 2012 and June 2015. All of the patients provided written informed consent. The Institutional Review Board (IRB) of Riyadh National Hospital approved the study.

Patients were included if they were adults (more than 18 years of age), of any gender, with chronic reflux symptoms and endoscopically-diagnosed BE. Patients were excluded if they have dysphagia, (barium study was done 1st to exclude stricture) or if were unfit, or non-willing to do gastrointestinal endoscopy.

Patients’ demographic data, history and examination findings including endoscopic findings were recorded.

Helicobacter pylori (H. pylori) was diagnosed by histopathological examination of gastric biopsy which is the gold slandered for diagnosis, 2 antral biopsies were taken (17), the presence of BE was diagnosed by WLE was reported as extension of salmon colored mucosa into esophagus > 1 cm proximal to the gastroesophageal junction (18). Multiple biopsies (four quadrant biopsies every 2 cm, together with targeted biopsies of visible lesions -Seattle protocol) were taken for histopathological confirmation, Positive BE was determined by presence of columnar-lined intestinal metaplasia in esophageal biopsies (19).

Patients whose histopathological examination revealed no BE [no=17], were reexamined and biopsied by NBI-targeted biopsy for detection of Barrett’s mucosa by histopathology, based on histopathology results, patients were divided into 2 groups, group 1 (BE positive, 80 patients) and group 2 (BE negative, 10 patients)

**Statistical analysis:**

SPSS, version 18 (SPSS Inc. Chicago, IL), was used, independent T test, Chi-square test were used for analysis

**Results:**

The study included 274 patients with chronic reflux symptoms, 90 patients had columnar-lined epithelium (CLE) (endoscopic BE) by WLE (32.8%), they were 67 males and 23 females with mean age 54.63 years.

Columnar-lined intestinal metaplasia was used to diagnose BE by histopathological examination, it was detected in 80 patients of those with endoscopic BE (group 1), mean age for patients with BE was 43.3 ± 11.07, which was higher than patients with negative BE (30.3±10.8), however, the difference was statistically insignificant (P: 0.56)

Age distribution of group 1 patients (positive BE) showed increased detection rates in age.
> 30 years, most of cases tested negative for BE (group 2) were in younger age group (below 30) (figure 1)

Sex distribution showed predominance of male patients in group 1 patients (62 males versus 18 females), while in group 2, male to female ratio was 1:1 (table 1).

Body Mass Index (BMI) was higher in group 1 patients (29.2±6.8) than group 2 patients (27.3±7), but the difference was statistically insignificant (P: 0.7) (table 1). Whereas obesity was more frequent in group 1 patients (75%), while 25% of them were either normal or underweight (table 2).

H pylori test was positive in 19 of group 1 patients, and 3 of group 2 patients, while most of patients with endoscopic BE tested negative for H pylori (68 patients out of 90 patients) (table 2).

Seventy-three patients- out of the ninety patients showed endoscopic BE, confirmed to have intestinal metaplasia by histopathology, biopsies were taken as 4 quadrant biopsies every 2 cm, together with targeted biopsies of visible lesions (Seattle protocol) (81.1% of cases with endoscopic BE, and 26.6% of all screened patients). 17 patients with negative histopathology for BE were re-examined endoscopically and NBI - targeted biopsies were taken for detection of BE, 7 patients of them proved to have columnar- lined intestinal metaplasia, so total patients confirmed to have BE has risen to 80 patients, out of 90 patients with endoscopic BE (88.9%). (figure 2).

**Figure (1):** Flow chart of the studied cases
Table (1) showed no statistically significant difference in the distribution of age and sex between those with and without BE. Table (2) showed no statistically significant difference in the distribution of positive Helicobacter pylori infection, BMI (kg/m$^2$), and BMI categories between those with and without BE. Table (3) showed that performing NBI-targeted biopsy following negative result of WLE-based biopsy for cases with endoscopically suspected BE increases the detection of BE from 81.1% to 88.9%. Although this did not achieve a statistical significance, it is of clinical concern.

### Table (1): Age and sex distribution in the studied cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (BE confirmed)</th>
<th>Group 2 (BE not confirmed)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>80</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age (yrs) mean±std</td>
<td>43.3±11.1</td>
<td>30.3±10.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (77.5%)</td>
<td>5 (50%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Female</td>
<td>18 (22.5%)</td>
<td>5 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Data expression [Test of significance]: N (%) [Fisher’s exact test] for sex and mean ± SD [Independent-Samples t-test] for age.

### Table (2): H. pylori status and BMI in the studied cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>80</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Positive H. pylori</td>
<td>19 (23.8%)</td>
<td>3 (30%)</td>
<td>0.72</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>29.2 ± 6.8</td>
<td>27.3 ± 7.02</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1 (1.3%)</td>
<td>1 (10%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Normal weight</td>
<td>19 (23.8%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>60 (75%)</td>
<td>8 (80%)</td>
<td></td>
</tr>
</tbody>
</table>

Data expression [Test of significance]: N (%) [Fisher’s exact test] for H. pylori and BMI categories and mean ± SD [Independent-Samples t-test] for age.

### Table (3): Detection of BE by WLE-based biopsy alone (WLE) vs. WLE-based biopsy followed by NBI-targeted biopsy for cases negative by WLE-based biopsy (WLE/NBI).

<table>
<thead>
<tr>
<th>BE</th>
<th>WLE</th>
<th>WLE/NBI</th>
<th>$\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>73 (81.1%)</td>
<td>80 (88.9%)</td>
<td>2.135</td>
<td>0.144</td>
</tr>
<tr>
<td>Negative</td>
<td>17 (18.9%)</td>
<td>10 (11.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data expression [test of significance]: N (%) [Chi-Square test].
Discussion:

The diagnosis of GERD is associated with a 10-15% risk of BE,20 the concept of metaplasia-dysplasia-carcinoma progression sequence in BE has led to the hypothesis that screening for BE, endoscopic surveillance to detect dysplasia, followed by endoscopic intervention, will lead to a decreased incidence of esophageal Adenocarcinoma (21) Preliminary studies suggest that NBI may represent significant improvement over standard endoscopy for detection of intestinal metaplasia within the BE segment and distinguish early neoplasia from nondysplastic BE (22)

This study was conducted to determine the role of NBI versus conventional white light endoscopy (WLE) in diagnosis of Barrett’s esophagus in patients with chronic gastroesophageal reflux diseases.

The absolute age-specific yield of Barrett’s esophagus in any particular group is poorly known in other studies, (23,24,25,26). However, in our studied patients, BE were detected more with increasing age (> 30 years), this also was agreed on by other studies where Barrett’s esophagus was diagnosed more commonly among older adults than younger adults,(27-30) BE occurs as a consequence of longstanding exposure of lower esophageal mucosa to acid reflux in cases with chronic GERD, which can explain development of BE in late adult and elderly, this may be an important point to define the best time of screening of patients with chronic GERD for the development of BE.

In our study, male gender was much more common than female gender in BE positive cases, this observation that male gender is an
independent risk factor for esophagitis is supported by other studies (31,32,33), which also raise the concern of screening of BE more in male patients as it can be considered as a risk factor for development of BE. A recent meta-analysis study on Barrett's esophagus shows a case mix of men and women of approximately 2:1. Whether this male preponderance is the result of differences between men and women in hormonal effects on the esophagus, body fat distribution, or other as-yet unidentified factors is not clear (34).

Obesity was found to be more frequent in our studied patients with BE (75%), this was supported by other previous studies which have suggested an association between abdominal obesity and risk of BE (35-38). For any given body mass index, subjects with higher amounts of intra-abdominal obesity, appear to have an increased risk of Barrett's esophagus. In a recent analysis of body anthropometry in subjects with Barrett's esophagus, body mass index was no longer an independent predictor of BE once waist-to-hip ratio was factored (39). Whether the increased risk associated with intra-abdominal obesity is due to mechanical or hormonal factors or a consequence of yet-undescribed factors is not known.

In our study, *H. pylori* test was positive in 19 of group 1 patients, and 3 of group 2 patients, while most of patients with endoscopic BE tested negative for *H pylori* (68 patients out of 90 patients) (table 2). This agreed with other studies that reported a strong inverse association between *H. pylori* and BE (0.36; 95% CI: 0.14–0.90), and this inverse association was explained by lower gastric-acid secretion associated with *H. pylori* which may be attributed to corpus atrophy or use of antisecretory medication (40, 41).

Of all screened patients, 90 (32.8%) patients had endoscopic BE, 80 patients had columnar-lined intestinal metaplasia. Seventy-three patients of them was diagnosed using 4 quadrant biopsies (81.1% of cases with endoscopic BE, and 26.6% of all screened patients), 17 patients with negative BE were re-examined and biopsied by NBI-targeted biopsies, 7 patients of them proved to have BE.

BE prevalence in the published literature has varied based on the definition of BE used, biopsy protocol, and the study population. One study detected BE in ~ 15% of patients with chronic GERD (42), in another study of patients with dyspepsia, only 5% were found to have CLE, whereas CLE with intestinal metaplasia was present in 2.4%.(43) Also other study evaluated patients undergoing
screening colonoscopy for CLE with intestinal metaplasia by upper endoscopy (44). The prevalence of CLE with intestinal metaplasia in those with heartburn was about 8.3%. Although these studies reported a much lower prevalence of BE, they lacked a definite biopsy protocol, besides choosing patients with different clinical diagnosis (dyspepsia in the 2nd study), and in the last study although they used a well-defined biopsy protocol, the study sample was biased toward those undergoing screening colonoscopy.

Use of NBI targeted biopsies to re-evaluate the presence of BE in patients with negative histopathology has increased the total number of diagnosed cases with BE from 81.1% to 88.9%, hence we concluded that performing NBI-targeted biopsy following negative result of WLE-based biopsy for cases with endoscopically suspected BE increases the detection of BE from 81.1% to 88.9%, although this did not achieve a statistical significance, it is of clinical concern (table 3, figure2). This may signify the role of NBI in accurately detecting the best site for biopsy taking to decrease sampling error and number of biopsies taken as in 4 quadrant- random biopsy technique.

In agreement with our results, another study concluded that NBI improves the visualization of important structures seen in BE over conventional endoscopy. Another study compared the use of high-resolution magnified NBI with conventional WLE with magnification in patients with BE, they found that the prediction of histology in NBI group was significantly higher than conventional WLE group (46)

For evaluation of number of biopsies taken, a study found higher rate for detecting dysplasia with NBI- targeted biopsy compared with conventional endoscopy with four-quadrant biopsy technique (47). However, in another study comparing high-resolution WLE with NBI in detecting early neoplasia, (48). Interestingly, the image quality was significantly better in the NBI group over the WLE group, but NBI was not found to improve the diagnostic yield of neoplasia. As they used different parameter to assess (neoplasia and not BE) this may explain the different outcome compared to our results

**Conclusion:**

NBI targeted biopsy could diagnose cases with BE missed by conventional endoscopy and decrease sampling error with fewer number of biopsies taken in the 4- quadrant random biopsy technique

**Recommendations:**

large, multicenter studies are needed for more characterization of the lesions by NBI and
correlation with the degree of dysplasia.

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