

Seattle protocol vs narrow band imaging guided biopsy in screening of Barrett's esophagus in gastroesophageal reflux disease patients

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Abstract

Barrett's esophagus has 0.5% to 7% risk of progression to esophageal adenocarcinoma. The method of obtaining biopsies to diagnose Barrett's is challenging. Seattle protocol has been considered as the gold standard, however its difficulty limits its applicability in practice. Narrow band imaging guided biopsy has been proposed as an alternative.

To investigate the accuracy, sensitivity, specificity and applicability of Narrow band guided biopsy as a screening tool for Barrett's esophagus in gastroesophageal reflux patients.

Endoscopy was done in 2 different sessions 2 weeks apart for 100 patients in Alexandria, Egypt. Patients had at least one of the following: Chronic Gastroesophageal reflux disease, frequent Gastroesophageal reflux disease, or two or more risk factors for Barrett's esophagus. All patients with known Barrett's esophagus were excluded.

Seventeen patients had Barrett's esophagus either by one of the two techniques or by both, 4 patients by both methods, 7 patients by narrow band imaging alone and 6 patients by Seattle protocol alone ($P < .001$, $\kappa = 0.461$). Sensitivity, specificity, negative predictive value and positive predictive value for Seattle protocol were 58.8%, 100%, 92.2%, 100% vs 76.5%, 100%, 95.4%, 100% respectively for narrow band imaging. A mean of 7.73 samples/patient was taken in Seattle protocol vs 3.42 samples in narrow band imaging ($P < .001$). A mean of 8.63 minutes was consumed in Seattle protocol vs 2.65 minutes in narrow band imaging ($P < .001$).

Narrow band imaging guided biopsy might have higher accuracy, sensitivity and negative predictive value as well as fewer number of biopsies and shorter time of the procedure compared to Seattle protocol which might increase its applicability as screening protocol for Barrett's esophagus. However, further larger multicentric studies are needed.

Abbreviations: BE = Barrett's Esophagus, BING = Barrett International NBI Group, EAC = esophageal adenocarcinoma, GERD = gastroesophageal reflux disease, NBI = narrow band imaging, SPSS = statistical package for the social sciences.

Keywords: Barrett's esophagus, narrow band imaging, screening, Seattle protocol

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.^[1] It is considered

the most common cause of heartburn with a prevalence ranging from 8.7% to 33% in the Middle East and 18.1% to 27.8% in North America.^[2]

One of the most critical GERD complications is the development of Barrett's esophagus (BE) which was first identified by N.R. Barrett in 1950^[3] and currently defined as intestinal metaplasia within the tubular esophagus with goblet cells and considered as the strongest risk factor to esophageal adenocarcinoma (EAC)^[4] which has a very poor prognosis^[5] and its incidence -especially in Europe and North America- is rapidly rising. It is estimated that 10% diagnosed with GERD has BE with 0.5% to 7% risk of progression to EAC depending on the presence/absence of dysplasia and its degree.^[6]

Evidence supports that surveillance of BE warrants early detection of EAC with better prognosis.^[7] Though, screening for BE in general population is not recommended by various societies/colleges of gastroenterology, the need to do selective screening in GERD patients with certain risk factors is widely accepted but inclusion criteria varies from one society/college to another.^[5] Near the end of 2015, American college of gastroenterology released a practice guideline focusing on diagnosis and management of BE. This guideline stated that patients who are indicated for screening of BE are men with chronic GERD (GERD for more than 5 years), and/or frequent GERD symptoms (GERD at least once/week) and two or more risk factors for BE or EAC which are old age (more than 50), Caucasian race, central obesity, current or past history of smoking,

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and positive family history of BE or EAC in a first-degree relative. The guideline stated also that screening for women shall be considered in the presence of multiple risk factors.^[6]

It is well established that BE is diagnosed only with endoscopic finding of salmon-colored mucosa in the esophagus with histopathological confirmation of intestinal metaplasia.^[6,8] The challenge in diagnosis of BE is the method of obtaining esophageal biopsies for histopathological examination. Since there is no specific features in white light endoscopy for BE, Seattle protocol described as targeted and random four-quadrant biopsies every 2 cm has long been considered as the gold standard of screening and surveillance of BE to minimize sampling error.^[9] However, difficulty of this protocol limits its applicability in practice in general and of course in screening of BE.^[10]

Recently other endoscopic imaging modalities have been proposed to obtain guided biopsies for BE screening/surveillance instead of Seattle protocol like chromo endoscopy and narrow band imaging (NBI). NBI improves the resolution by changing wavelength so that white light is restricted to blue light, which is better absorbed by hemoglobin, allowing better visualization of subtle and small lesions.^[11]

Previous studies have studied the utility of NBI guided biopsy vs White light Seattle protocol in BE surveillance, showing promising results in prediction of histology compared to Seattle protocol.^[12,13] However, its rule, accuracy and applicability in screening for BE in GERD patients with no known BE has not been studied in a dedicated study before.

2. Patients and methods

2.1. Patients and study design

A prospective study was held in a tertiary care endoscopy unit in Alexandria, Egypt to compare the number of biopsies needed and time consumed by each imaging technique in addition to

sensitivity, specificity, negative predictive value, positive predictive value and accuracy of BE detection by the 2 techniques. The study was reviewed and approved by the local ethics committee in accordance with the ethical standards laid down in declaration of Helsinki.

One hundred patients scheduled for upper gastrointestinal tract endoscopy were included after taking informed written consent from the patients. Inclusion criteria were clinical diagnosis of GERD, presence of endoscopic esophagitis and at least one of the following criteria:

1. Chronic GERD (more than 5 years).
2. Frequent GERD (weekly or more).
3. Two or more risk factors for BE or EAC: Old age >50 years, central obesity (waist circumference >102 cm in males and >88 cm in females), current or past history of smoking and family history of BE or EAC.

Exclusion criteria included: History of known Barrett's esophagus, age younger than 18 years old, pregnancy, esophageal varices, severe uncontrolled coagulopathy and history of upper gastrointestinal surgeries.

2.2. Procedure

After taking a brief history from every patient including age, sex, indication for endoscopy and ruling out any patient that has any of the exclusion criteria, upper gastrointestinal endoscopy was done by a single endoscopist in 2 different sessions 2 weeks apart from each other to allow mucosa to heal. In the first session Seattle protocol (targeted and random four-quadrant biopsies every 2 cm) was applied. After 2 weeks endoscopy was repeated for every patient and biopsies guided by NBI from suspicious lesions were taken. Suspicious lesions were defined as follows: in Seattle protocol mucosal irregularities (e.g., nodules/ulcers)

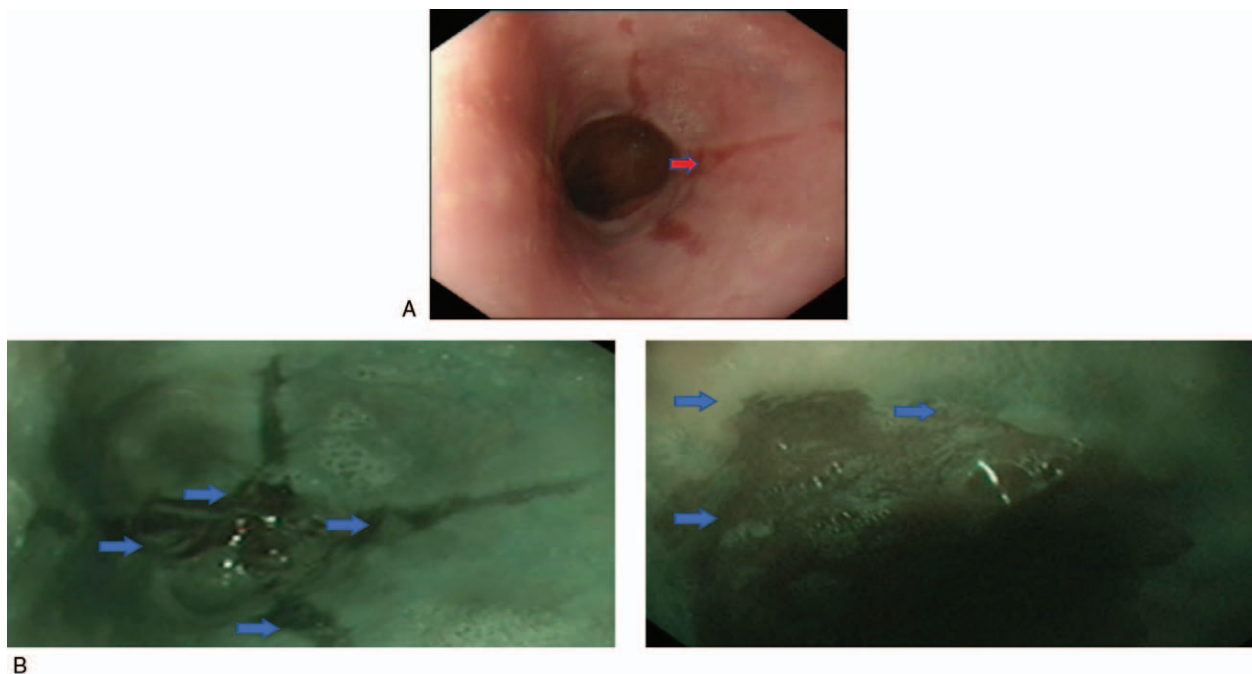


Figure 1. A- GERD Los Angeles Class B with mucosal irregularity (red arrow) by white light endoscopy. B- GERD with irregular mucosal pattern (blue arrows) by narrow band imaging. GERD = gastroesophageal reflux disease.

(Fig. 1A),^[14] in NBI suspicious lesions were defines as per Barrett International NBI Group (BING) classification as any lesion with irregular/absent mucosal pattern and/or any lesion with irregular vascular pattern defined as focally or diffusely distributed vessels not following normal architecture of the mucosa^[15] (Fig. 1B). Patients were sedated according to standard protocols, upper GIT endoscopy for all patients was done using standard single use biopsy forceps. All biopsies were embedded in paraffin, sectioned, stained with hematoxylin and eosin and then reviewed by a single pathologist who was blinded to the endoscopy results. Histologic findings were classified according to the revised Vienna classification of gastrointestinal neoplasia.^[16]

2.3. Statistical analysis

We used Statistical Package for the Social Sciences (SPSS) 22 (2013; IBM, US). Chi-square test/Fisher exact test were used as tests of significance for independent dichotomous data with kappa (κ) as a measure for agreement, and paired *t* test was used for continuous paired data. *P* value of <.05 was considered statistically significant.

3. Results

Of the 100 GERD patients included from September 2017 to end of March 2018, 60% were males and 40% females with mean age of 47.7 ± 13.6 years old (range 18 to 75 years old).

Depending on Los Angeles endoscopic classification of GERD, 51 patients had GERD class A (51%), 35 patients had GERD class B (35%), 8 patients had GERD class C (8%), and 6 patients had GERD class D (6%).

Considering the overall worst diagnosis by histopathology as the true diagnosis (Gold standard), Of the 100 consecutive GERD patients, 17 patients were found to have BE (17%) either by one of the two techniques or by both, of them 6 patients showed BE from biopsies taken by Seattle technique and NBI guided biopsy (6%), 7 showed BE from biopsies taken by NBI guided biopsy alone (7%), and 4 patients diagnosed by biopsies taken by Seattle technique alone (4%). This difference in detection rate was found to have high statistical significance with a moderate level of agreement ($P < .001, \kappa = 0.461$) (Table 1).

Sensitivity, specificity, negative predictive value and positive predictive value for Seattle protocol were 58.8%, 100%, 92.2%, 100% respectively vs 76.5%, 100%, 95.4%, 100% respectively for NBI guided biopsy. Accuracy of Seattle protocol was 93% vs 96% for NBI guided biopsy.

On comparing total number of samples taken by Seattle protocol vs taken by NBI guided biopsy, a total of 773 samples were taken by Seattle protocol vs 342 samples were taken by NBI guided biopsy, ranging from 3 to 14 samples per case taken by

Seattle protocol vs 1 to 8 samples per case taken by NBI guided biopsy with a mean of 7.73 ± 3.09 for Seattle protocol vs 3.42 ± 1.33 for NBI guided biopsy. This difference was found to have a high statistical significance ($P < .001$) (Fig. 2).

On comparing also the time consumed during Seattle protocol vs time taken by NBI guided biopsy, considering that time was calculated in minutes from beginning of introducing biopsy needle in to the endoscope channel till totally removing the needle from the endoscope, the time of the procedure ranged from 5.6 to 12.6 minute per case taken by Seattle protocol vs 1 to 4.4 minute per case taken by NBI guided biopsy with a mean of 8.63 ± 1.84 minutes for Seattle protocol vs 2.65 ± 0.96 minutes for NBI guided biopsy and this difference was also found to have a high statistical significance ($P < .001$) (Fig. 3).

4. Discussion

In our study, we compared the utility of NBI guided biopsy vs Seattle protocol in screening for BE in 100 GERD patients in terms of accuracy of detecting BE in histopathological examination, number of samples taken, time consumed by endoscopist to take biopsies by both methods.

Regarding accuracy and applicability of Seattle protocol vs NBI guided biopsy in diagnosis of BE and dysplasia, it was shown in our study that, 10 (58.8%) out of the 17 BE patients detected were diagnosed by Seattle protocol vs 13 (76.5%) by NBI guided biopsy and this difference in detection rate was found to have a high statistical significance with a moderate level of agreement ($P < .001, \kappa = 0.461$). Sensitivity, specificity, negative predictive value and positive predictive value for Seattle protocol were shown to be 58.8%, 100%, 92.2%, 100% respectively with an accuracy of 93% vs 76.5%, 100%, 95.4%, 100% respectively for NBI guided biopsy with better accuracy of 96%.

In agreement to our study, in 2016 a study performed on 84 Romanian patients doing endoscopy for screening or surveillance of BE showed that the sensitivity, specificity, negative predictive and positive predictive values of standard endoscopy in detecting BE were lower than NBI guided biopsy.^[17] On the other side Sharma et al,^[12] found that both Seattle protocol and NBI guided biopsy has the same detection rate of BE, however this result might be explained by using high definition white light endoscopy as well as magnified NBI Vs standard white light endoscopy and non-magnified NBI in our study.

Beside higher detection rate of NBI guided biopsy vs Seattle protocol, our study found that NBI guided biopsy required lower number of samples per case (a mean of 3.42 ± 1.33 for NBI guided biopsy vs 7.73 ± 3.09 for Seattle protocol) and shorter time to take biopsies (a mean of 2.65 ± 0.96 minutes for NBI guided biopsy vs 8.63 ± 1.84 minutes for Seattle protocol), and these differences in number of samples per case and time

Table 1

Relation between results of biopsies taken by Seattle protocol and NBI guided biopsy (n=100).

Diagnosed by NBI guided biopsy	Diagnosed by Seattle protocol				F _p
	Barrett's		Non-Barrett's		
	No.	%	No.	%	
Barrett's	6	60.0	7	7.8	P < .001
Non-Barrett's	4	40.0	83	92.2	

F_p: Fisher Exact.

NBI=Narrow band imaging.

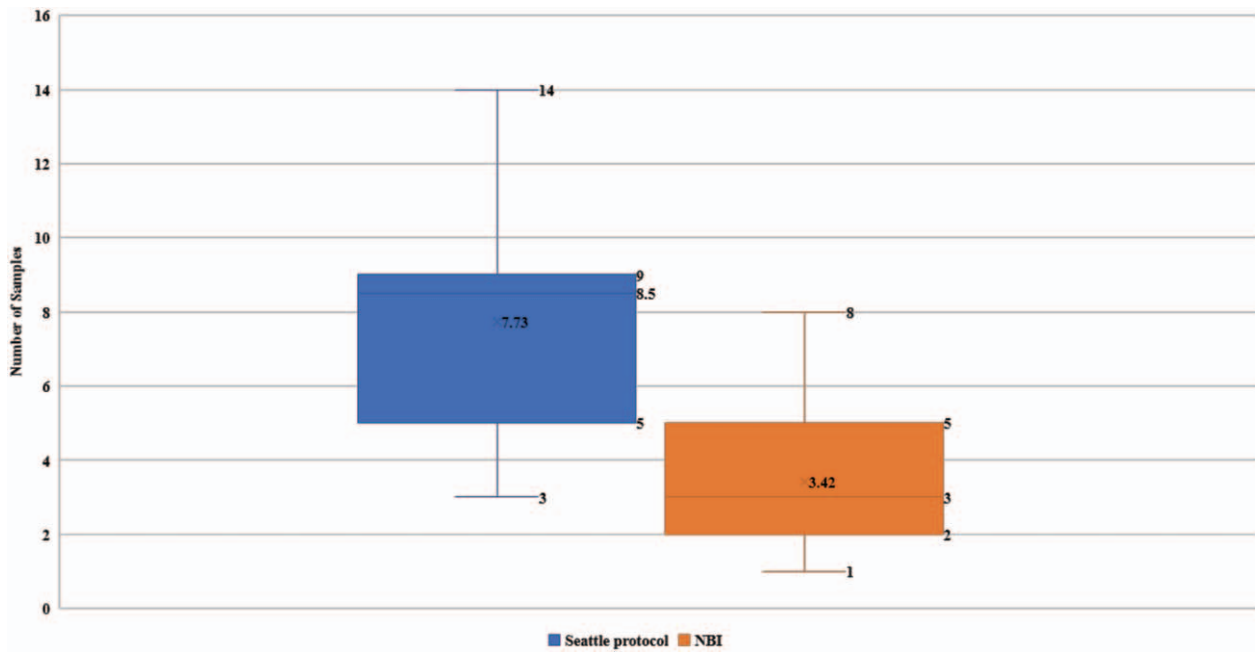


Figure 2. Number of samples taken by Seattle protocol and narrow band imaging.

consumed were found to have a high statistical significance ($P < .001$).

To the best of our knowledge, this is the first study to compare the time consumed by both techniques. However, regarding the number of samples, our study agrees with the study of Sharma et al,^[12] which showed that white light endoscopy required a mean of 7.6 samples/patient vs NBI which required a mean of 3.6 samples/patient to detect BE ($P < .001$). Pascarenco et al,^[17] also

showed that smaller number of biopsies taken by NBI guided biopsy compared to Seattle protocol (1.82 vs 3.04 respectively) are required to detect BE. However, the smaller number of samples in this study compared to our study is justified the high prevalence of short segment Barrett's in this study.

Our study didn't find any statistically significant difference in the detection rate of dysplasia between the two techniques. This disagree with most of the studies in the literature,^[12-14] however this is

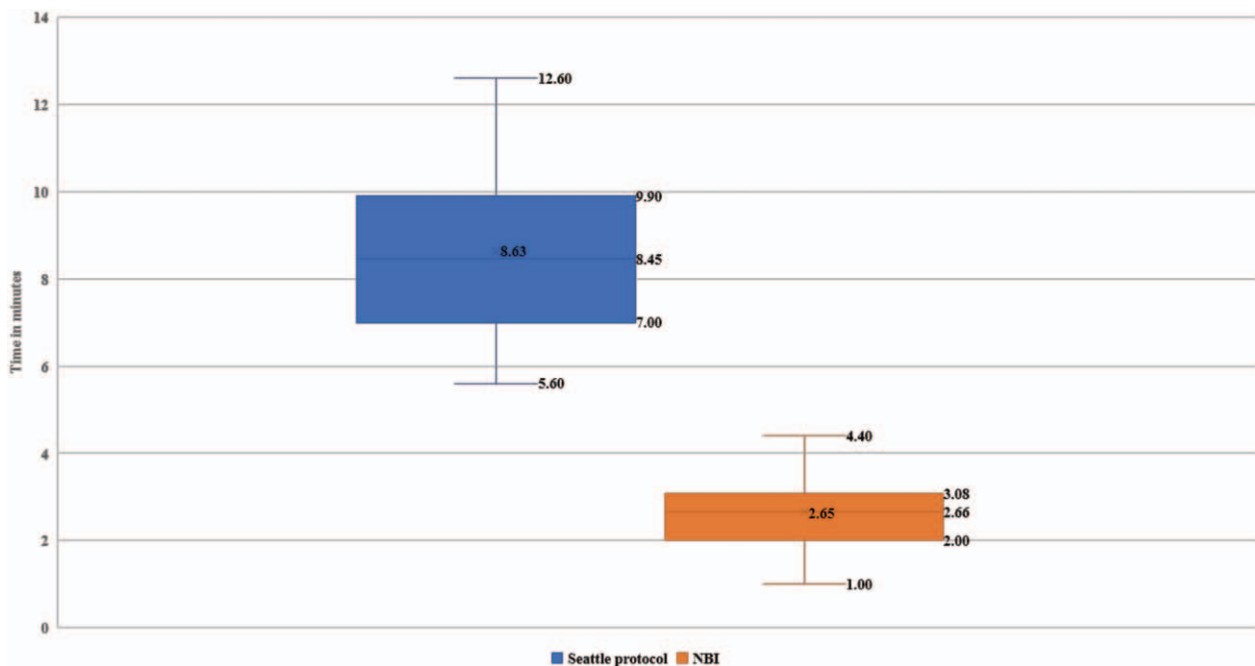


Figure 3. Time consumed during performing both techniques.

explained that the aim of most of the previous studies was to study the utility of NBI as surveillance tool in patients with known BE.

There are some limitations to this study, the relatively small number of BE patients makes it difficult to draw a definite conclusion regarding the superiority of NBI guided biopsy. The lack of magnifying NBI also led to some difficulty in detection of abnormal vascular pattern as stated by BING classification, and almost all suspicious lesions sampled were due to presence of irregular mucosal pattern only. These drawbacks may limit the reproducibility of our study. However, this study shows that even with the lack of high definition white light endoscopy and magnifying NBI, NBI guided biopsy might have superior results and this may be beneficial specially for endoscopy units in developing countries that lack such advanced technology.

5. Conclusions

Our study compared the utility of NBI guided biopsy Vs Seattle protocol as a screening tool to detect BE in GERD patients. Despite the relatively small sample size, NBI guided biopsy showed higher ability to detect BE than Seattle protocol with higher overall accuracy, sensitivity and negative predictive value, requiring smaller number of biopsies and shorter time of the procedure compared to Seattle protocol to achieve these results which might increase its applicability as screening protocol and the compliance of physicians from one side, and might also decrease the complications of endoscopy from the other side. However further multicentric larger multicentric studies are still required.

Author contributions

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