Benefits of the Seattle biopsy protocol in the diagnosis of Barrett’s esophagus in a Chinese population

Shou-Wu Lee, Han-Chung Lien, Chi-Sen Chang, Ming-Xian Lin, Chung-Hsin Chang, Chung-Wang Ko

Case Control Study

AIM
To investigate the benefits of the Seattle protocol in the diagnosis of Chinese individuals with Barrett’s esophagus.

METHODS
Subjects enrolled were patients from one center with endoscopically-suspected esophageal metaplasia. These patients first received narrow-band imaging-targeted biopsy, and later, the Seattle protocol-guided biopsy, within a period from October 2012 to December 2014. Those cases without initial pathologic patterns of intestinal metaplasia (IM) and then appearance or loss of IM tissue were designated as Group A or B, respectively. Those with initial pathologic patterns of...
IM, which then persisted or were lost were designated as Group C or D, respectively.

RESULTS
The number of cases for each group was as follows: A: 20, B: 78, C: 31 and D: 14. The distribution of the Prague criteria M levels of Group A was significantly higher than Group B ($P = 0.174$). Among these groups, Group C had the highest proportions of hiatus hernia (54.8%), long segment Barrett’s esophagus (29%), and also the highest Prague criterion M levels. The sensitivity of IM detection was 69.2% for the narrow-band imaging-targeted biopsy and 78.5% for the Seattle protocol-guided biopsy. The difference was not significant ($P = 0.231$). The number of detectable dysplasias increased from one case via the NBI-target biopsy to five cases via the Seattle protocol-guided biopsy, including one case of adenocarcinoma.

CONCLUSION
The Seattle protocol improved the IM detection in our subjects with higher Prague criteria M levels and disclosed more cases with dysplastic tissues.

Key words: Barrett’s esophagus; Dysplasia; Intestinal metaplasia; Seattle protocol; Chinese

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Core tip: While comparing the diagnosis of Barrett’s esophagus in a Chinese population via narrow-band imaging-targeted biopsy or the Seattle protocol-guided biopsy, the sensitivity of intestinal metaplasia detection was 69.2% and 78.5%, respectively. The number of detectable dysplasias increased from one case via the narrow-band imaging-targeted biopsy to five cases via the Seattle protocol-guided biopsy. These results concluded that the Seattle protocol identified more cases with dysplastic tissues.

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INTRODUCTION
Endoscopically, the current definition of Barrett’s esophagus (BE) includes the presence of an area of salmon-colored mucosa in the distal esophagus, plus the histological finding of intestinal metaplasia (IM) in the esophagus[12]. BE is clinically important because it is a major risk factor for the development of esophageal adenocarcinoma (EAC), and the number of EAC cases has been growing in Western countries[21]. EAC is typically diagnosed at an advanced stage when it also has a poor prognosis, as its 5-year survival rate is low (17%)[3]. Therefore, early detection of BE, especially those with dysplastic tissue, attracted recent research interests. Regarding the choice of biopsy methods in detecting BE, the use of narrow band imaging (NBI) has been compared with traditional white light endoscopy (WLE), and results showed its superiority over WLE[1,2,3]. According to the American Gastroenterological Association guidelines, the standard for diagnosing BE is the endoscopic evaluation performed with 4-quadrant biopsy specimens taken every 1-2 cm, which is described as the Seattle biopsy protocol[1,4]. However, some in this field considered disadvantages of the Seattle protocol as being relatively inefficient, time-consuming and providing a low diagnostic rate[5-7]. In Europe, reportedly only half of endoscopists follow the Seattle protocol for biopsy of BE patients[8,9].

Our present study was aimed to evaluate the benefits of the Seattle protocol on BE cases in a Chinese population of Taiwan.

MATERIALS AND METHODS

Subject collection
We collected data from subjects who had endoscopically-suspected esophageal metaplasia followed by NBI-targeted biopsy conducted at the Medical Screening Center at Taichung Veteran General Hospital. Over a period from October 2012 to December 2014, these patients were asked to repeat another open-access transoral upper gastrointestinal endoscopy together with the Seattle protocol-guided biopsy. NBI-target biopsy was defined as surveillance of the gastroesophageal junction (GEJ) with NBI, and a biopsy was taken according to the individual endoscopist’s expertise. Seattle protocol-guided biopsy was performed with 4-quadrant biopsy specimens taken every 1-2 cm at the GEJ. We recorded the general patient data, which included their age, gender, and body mass index (BMI). In addition, we collected their endoscopic findings, including hiatus hernia, erosive esophagitis (EE), short segment BE (SSBE, extending < 3 cm into the esophagus) and long segment BE (LSBE, extending ≥ 3 cm into the esophagus)[10], the Prague C and M criteria[11], and pathologic dysplasia appearances, including low-grade dysplasia (LGD), high grade dysplasia and EAC.

Exclusion criteria
Exclusion criteria included total esophagectomy, severe cardiopulmonary deficiency, malignancy, other unsuitable conditions for upper gastrointestinal scope, and segments of metaplastic columnar epithelium < 1 cm, which were classified as “specialized IM of the esophagogastric junction”.

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Table 1  General data and endoscopic appearances of groups A and B

|               | Group A (n = 20) | Group B (n = 78) | P-value |
|---------------|------------------|------------------|---------|
| Age (yr)      | 60.95 ± 17.29    | 55.19 ± 13.28    | 0.189   |
| Gender (male) | 9 (45.0)         | 35 (44.9)        | 0.992   |
| BMI (kg/m²)   | 25.76 ± 4.52     | 23.69 ± 5.59     | 0.079   |
| EE            | 7 (35.0)         | 15 (19.2)        | 0.132   |
| Hiatus hernia | 8 (40.0)         | 15 (19.2)        | 0.051   |
| LSBE          | 2 (10.0)         | 3 (3.8)          | 0.269   |
| Biopsy pieces | 4.58 ± 1.57      | 3.39 ± 1.74      | 0.009   |

1P-values were analyzed with t-test; 2P-values were analyzed with Pearson’s χ² test. BMI: Body mass index; EE: Erosive esophagitis; LSBE: Long segment Barrett’s esophagus.

RESULTS

From the total of 143 enrolled subjects, the number of patients in each group was as follows: A: 20 (14%), B: 78 (54.5%), C: 31 (21.7%) and D: 14 (9.8%).

First, for Groups A and B, their general data and endoscopic appearances are shown in Table 1. The levels of age, gender and BMI were similar between the two groups. Compared to Group B, Group A had slightly higher proportions of EE (35% vs 19.2%, \( P = 0.132 \)), hiatus hernia (40% vs 19.2%, \( P = 0.051 \)), and LSBE (10% vs 3.8%, \( P = 0.269 \)), but none of the differences were statistically significant. However, we found significantly more endoscopic biopsy pieces at the GEJ in Group A than in Group B (mean 5.69 vs 4.00, \( P = 0.039 \)). The Prague C and M criteria of these subjects in Groups A and B are shown in Figure 2A. The distributions of “C” levels were similar between groups (\( P = 0.174 \)), but the “M” levels were significantly higher in Group A (\( P = 0.021 \)).

The general data, endoscopic appearances and the Prague C and M criteria for Groups C and D are shown in Table 2 and Figure 2B. Group C had, among all groups, the highest proportion of hiatus hernia (54.8%), LSBE (29%) and the highest Prague criteria “M” levels. Group D, compared to Group C, had a significantly higher proportion of EE (57.1% vs 19.4%, \( P = 0.011 \)) and fewer biopsy pieces (mean 4 vs 5.69, \( P = 0.039 \)).

The results of the two different biopsy protocols in terms of sensitivity of IM detection are listed in Table 3. Among all subjects with pathologic appearance of IM at the GEJ (\( n = 65 \) in Groups A, C and D), 45 of them (in Groups C and D) yielded positive IM results via NBI-target biopsy at a sensitivity of 69.2%. In comparison, 51 subjects (in Groups A and C) yielded positive IM results via the Seattle protocol-guided biopsy, with a higher sensitivity of 78.5%. However, the difference of IM detection rates between these two biopsy protocols was not significant (\( P = 0.231 \)).

As shown in Table 3, the number of detectable dysplasias in the GEJ of all the enrolled subjects was only one case at the beginning with NBI-target biopsy, which later increased to five cases using the Seattle protocol. Among the five subjects, four were LGD and
one was EAC arising from the BE tissue.

**DISCUSSION**

BE, a condition in which the squamous epithelium of the distal esophagus is replaced by columnar epithelium with IM, is a well-established precursor of EAC. Regarding the risk of EAC, BE has a > 40-fold increase over the general population. Although BE has been a disease primarily found in the Western world, it has become more frequently reported in Asian countries [12]. The underlying etiology of BE is still unclear. In the majority of cases, BE is associated with a combined reflux of acid and bile, even in the absence of symptoms. The prevalence of BE has been estimated at 1%–2% in patients undergoing endoscopy for any indication, and the prevalence rises to 5%–15% in patients with gastroesophageal reflux disease (commonly known as GERD) symptoms [13]. Risk factors for BE include older ages, male gender, Caucasian race, GERD symptoms, central abdominal obesity, and possibly tobacco smoking [14].

Due to the extremely poor outcome of EAC, the early and accurate diagnosis of BE, especially with the presentation of dysplastic tissue, is particularly important. Currently, the use of electronic chromoendoscopy, like NBI, is a standard protocol for detecting BE.

Table 2  General data and endoscopic appearances of groups C and D

|                      | Group C (n = 31) | Group D (n = 14) | \( P \)-value |
|----------------------|-----------------|-----------------|--------------|
| **Age (yr)**         | mean ± SD       | mean ± SD       |              |
| Gender (male)        | 66.53 ± 12.47   | 65.79 ± 14.18   | 0.860\(^1\) |
| BMi (kg/m\(^2\))     | 25.65 ± 3.70    | 23.14 ± 3.64    | 0.051\(^1\) |
| EE                   | 6 (19.4)        | 8 (57.1)        | 0.011\(^2\) |
| Hiatus hernia        | 17 (54.9)       | 6 (42.9)        | 0.457\(^3\) |
| LSBE                 | 9 (29.0)        | 2 (14.3)        | 0.287\(^3\) |
| Biopsy pieces        | 5.69 ± 2.82     | 4.00 ± 2.18     | 0.039\(^3\) |

\(^1\)\( P \)-values were analyzed with \( t \)-test; \(^2\)\( P \)-values were analyzed with Fisher’s exact test; \(^3\)\( P \)-values were analyzed with Pearson’s \( \chi^2 \) test.

Table 3  Results of the two different biopsy protocols \( n \) (%)

|                      | NBI-targeted biopsy | Seattle protocol-guided biopsy | \( P \)-value |
|----------------------|---------------------|-------------------------------|--------------|
| **IM (n = 65)**      | 45 (69.2)           | 51 (78.5)                     | 0.231\(^2\) |
| Dysplastic tissue    |                     |                               |              |
| Group A (n = 20)     | 0 (0.0)             | 2 (10.0)                      | 0.486\(^2\) |
| Group B (n = 31)     | 1 (3.2)             | 3 (9.6)                       | 0.612\(^2\) |
| Group C (n = 14)     | 0 (0.0)             | 0 (0.0)                       | 1.000\(^2\) |

\(^2\)\( P \)-values were analyzed with Fisher’s exact test; \(^3\)\( P \)-values were analyzed with Pearson’s \( \chi^2 \) test.

One adenocarcinoma in Group B detected via Seattle protocol guided biopsy. IM: Intestinal metaplasia; NBI: Narrow-band imaging.

Figure 2  Endoscopic appearances of the patients in Groups A and B (A), Groups C and D (B) according to the Prague C and M criteria.
also vulnerable to sampling errors, consequently lower diagnostic rates, suboptimal disease management, and poorer adherence to the practice guidelines[5-9].

In a multicenter, randomized, crossover trial of 123 BE patients, the NBI-targeted biopsy was compared with the 4-quadrant biopsy with WLE. No difference was found between the two techniques in terms of the frequency of detecting IM tissues (both 85%) and dysplasia (71% for NBI vs 55% for WLE; \( P = 0.15 \))[3]. However, the procedure of “4-quadrant biopsy” in that study is not fully compatible with the Seattle protocol. As a result, the IM or dysplasia detection rate might have been underestimated. Another study enrolling 2245 BE patients from the U.S. pathology database reported that only 51.2% of cases had adhered to the Seattle protocol, and more cases of LSBE were associated with poorer adherence. Furthermore, non-adherence was associated with fewer detections of dysplasia (OR = 0.53, 95%CI: 0.35-0.82)[3].

For our patients, the Seattle-protocol guided biopsy, when compared with NBI-target biopsy, slightly improved the sensitivity rate of IM at the GEJ (78.5% vs 69.2%), although the difference was not significant (\( P = 0.231 \)). Further analysis showed that the Seattle-protocol-guided biopsy had improved IM detection in those cases with higher “M” levels, according to the Prague criteria. On the contrary, the Seattle biopsy protocol had limitations regarding the correct diagnoses of BE in those individuals with EE. Unsurprisingly, the more biopsy samples were obtained during endoscopy, the better the diagnosis of IM became. This could account for the lack of difference between these two biopsy protocols in detecting IM in most of our cases with LSBE, and support that the more biopsy pieces that were taken, the less likely sampling errors occurred.

The mean biopsy pieces obtained per patient in our study ranged between 3.39 and 5.69. The majority of cases with fewer biopsy pieces were SSBE (89.5%). This finding is compatible with previous studies on Asian patients[12]. According to one study, biopsies of at least eight pieces at the GEJ was required for an adequate diagnostic rate. The Seattle biopsy protocol. However, some in this field consider disadvantages of the Seattle protocol as being relatively inefficient, time-consuming and providing low diagnostic rates. In Western countries, reportedly only half of endoscopists follow the Seattle protocol for biopsy of BE patients.

One study in the UK enrolling 220 BE subjects reported a significant increase in the detection rate of all types of dysplasia when the Seattle Protocol was adapted (LGD: 12% vs 3.6%, advanced dysplasia: 5.2% vs 0.8%, \( P < 0.00001 \))[17]. In our study, the number of cases with dysplastic tissue over the GEJ increased from one via the NBI-target biopsy to five via the Seattle protocol-guided biopsy, although the increment was not significant. For the one patient with EAC detected early by the Seattle protocol-guided biopsy, treatments were started promptly with curative therapy, like the endoscopic submucosal dissection.

Recently, other advanced endoscopic techniques have been introduced to improve the detection of IM and dysplastic tissue in BE. These techniques include cysotosponge, esophageal capsule endoscopy, dye-based chromoendoscopy, and confocal laser endomicroscopy[18,19]. However, they have not yet reached routine clinical application due to their higher costs and uncertain efficacies.

There are some limitations in our study. Firstly, the endoscopic and pathologic appearance were diagnosed or confirmed by individual endoscopists and pathologists, with inevitable inter-observer and intra-observer variations. Secondly, this study was hospital-based and data were derived from a single tertiary care center. Selection bias of cases could not be ruled out. Thirdly, some BE-associated variables, like reflux symptom, smoking habit and Helicobacter pylori, were not analyzed. Finally, most of our cases belonged to SSBE, and this may not reflect populations in the Western countries. Further work is still needed to confirm or reinforce our present results.

In conclusion, we found that the Seattle protocol showed improvements in IM detection in subjects with high Prague criteria “M” levels, and disclosed more cases, including EAC, with dysplastic tissue.

**ARTICLE HIGHLIGHTS**

**Research background**

According to the American Gastroenterological Association guidelines, the definition of Barrett’s esophagus (BE) includes the histological finding of intestinal metaplasia (IM) in the esophagus. BE is clinically important because it is a major risk factor for the development of esophageal malignancy. Therefore, early detection of BE, especially those with dysplastic tissue, attracted recent research interests.

**Research motivation**

The standard for diagnosing BE is endoscopic evaluation performed with the Seattle biopsy protocol. However, some in this field consider disadvantages of the Seattle protocol as being relatively inefficient, time-consuming and providing low diagnostic rates. In Western countries, reportedly only half of endoscopists follow the Seattle protocol for biopsy of BE patients.

**Research objectives**

The aim of this study is to investigate the benefits of the Seattle protocol in the diagnosis of Chinese individuals with BE.

**Research methods**

Subjects enrolled were cases of Taichung Veterans General Hospital with endoscopically-suspected esophageal metaplasia. These patients first received the narrow-band imaging (NBI)-targeted biopsy and later the Seattle protocol-guided biopsy, within a period from October 2012 to December 2014. Cases without initial pathologic patterns of IM and then appearance or loss of IM tissue were designated as Group A or B, respectively. Those with initial pathologic patterns of IM, which then persisted or were lost were designated as Group C or D, respectively.

**Research results**

The number of cases for each group was as follows: A: 20, B: 78, C: 31 and D: 14. The distribution of the Prague criteria M levels of Group A was significantly higher than Group B (\( P = 0.174 \)). The sensitivity of IM detection was 69.2% for the NBI-targeted biopsy and 78.6% for the Seattle protocol-guided biopsy. The difference was not significant (\( P = 0.231 \)). The number of detectable dysplasia increased from one case via the NBI-targeted biopsy to five cases via the Seattle protocol-guided biopsy, including one case of adenocarcinoma.

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Research conclusions
The Seattle protocol improved the IM detection in the subjects with higher Prague criteria M levels, and it disclosed more cases with dysplastic tissues.

Research perspectives
In the future, the prospective studies in the selected BE patients should be conducted to evaluate the usefulness of the Seattle protocol in clinical practice.

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