Advances in imaging and endoscopic therapy in Barrett’s esophagus
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Narrow Band Imaging does not reliably predict residual intestinal metaplasia after radiofrequency ablation


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Abstract

**Introduction:** After radiofrequency ablation (RFA) of Barrett’s esophagus, it may be difficult to determine if complete eradication of intestinal metaplasia (IM) at the neosquamocolumnar junction (neo-SCJ) in the cardia is achieved. Narrow-band imaging (NBI) is claimed to predict presence of IM which would allow for immediate treatment. **Aim:** To evaluate if inspection with NBI of the neo-SCJ after RFA allows for reliable detection of IM. **Methods:** Patients with a normal appearing neo-SCJ scheduled for RFA were included. Two expert-endoscopists obtained images from the neo-SCJ in overview (high resolution white light and NBI) and from four areas with NBI zoom, followed by corresponding biopsies. Four other blinded expert-endoscopists evaluated the images for the presence of IM and type of mucosal pattern (“round”/“small tubular”/“large tubular”/“villous”). Endpoints were sensitivity and specificity for identifying patients and areas with IM. **Results:** From 21 patients overview images from 21 neo-SCJs and NBI zoom images from 83 neo-SCJ areas were obtained. IM was present in 5 (24%) overview images and 9 (11%) zoom images. Using the overview images sensitivity and specificity for identifying patients with IM were 65% (95%CI 38-86%) and 46% (95%CI 33-60%), respectively. For individual zoom images, sensitivity was 71% (95%CI 54-85%) and specificity 37% (95%CI 32-43%). **Conclusions:** After RFA, endoscopic inspection with NBI of the neo-SCJ in overview or zoom does not reliably predict presence or absence of IM.
Introduction

Barrett's esophagus is a condition of the distal esophagus in which the normal squamous epithelium has been replaced by columnar lined epithelium containing intestinal metaplasia upon biopsy. It is a premalignant condition in which esophageal advanced adenocarcinoma can arise through a multi-step transition sequence of neoplastic changes.

Endoscopic therapy is increasingly used for the treatment of early neoplasia in Barrett's esophagus. An important treatment modality is radiofrequency ablation (RFA) preceded if necessary by endoscopic resection.

Radiofrequency ablation of Barrett's esophagus usually requires multiple treatment sessions starting with circumferential ablation of the whole Barrett's segment, followed by focal ablation of remaining Barrett's epithelium every two to three months. In the majority of the patients complete endoscopic and histological eradication of intestinal metaplasia and neoplasia is achieved after one circumferential and two focal ablations. Ablation sessions are generally continued until no columnar epithelium is seen in the distal esophagus.

During this treatment protocol, it is difficult to assess if all Barrett's epithelium at the neosquamocolumnar junction (neo-SCJ) has been eradicated. Therefore, it is advised to take random biopsies immediately distal (<5mm) to the neo-SCJ in order to document complete histological eradication of intestinal metaplasia at this level after which patients will enter follow-up. The biopsies, however, may miss small residual areas of intestinal metaplasia, and the histology results are not readily available. A reliable endoscopic detection tool for residual intestinal metaplasia at the neo-SCJ in the cardia would overcome these drawbacks and would allow for immediate additional RFA treatment when complete eradication has not yet been achieved.

An endoscopic detection technique that might predict the presence of intestinal metaplasia is narrow-band imaging (NBI) as it allows for detailed inspection of the mucosal pattern. Several studies on magnification endoscopy with NBI have described and classified these mucosal patterns in Barrett's esophagus. Generally, round patterns are believed to be associated with gastric mucosa, while more complex branching patterns and villous patterns are believed to be associated with intestinal metaplasia (Figure 1).

The aim of this study was to evaluate if endoscopic inspection with NBI of the neo-SCJ after RFA allows for a reliable detection of residual intestinal metaplasia.
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Figure 1 Zoom images of mucosal patterns at the neosquamocolumnar junction in the narrow-band imaging mode with a “round” (A); “small tubular” (B); “large tubular” (C); and “villous” pattern (D).

Methods

Setting and patient selection
Images were prospectively and non-consecutively collected at the Academic Medical Center, Amsterdam, Netherlands, which is a tertiary referral center for the detection and treatment of patients with early neoplasia in Barrett’s esophagus. Patients were eligible when the following inclusion criteria were met: 1) patients scheduled for RFA after at least one prior session of RFA; 2) a normal appearing neo-SCJ at endoscopy, arbitrary defined as C≤1M≤1. The current study was considered a subanalysis of published and ongoing IRB approved RFA trials from our group (NTR1337, NTR1434, NTR1198 and NTR1211). All patients provided informed consent for these trials.

Endoscopic procedure and image collection
All endoscopic procedures were performed under conscious sedation with intravenous midazolam and supplemented with fentanyl if necessary. We used an RGB-based NBI-endoscopy system with magnification endoscopes (GIF-Q240Z/Q260Z/H260Z, Olympus Inc., Tokyo, Japan). A soft
distal attachment cap (Model MB-046, Olympus, Tokyo, Japan) was mounted on the tip of the endoscopes in order to fix the mucosa when obtaining the magnified still images. After rinsing with water and acetylcysteine (5%) to remove mucous, the neo-SCJ was inspected in overview with white light and with NBI. Images of the neo-SCJ were obtained in overview in the high resolution white light mode and the NBI mode. Subsequently, magnified still images were obtained in the NBI mode with approximately 50% of the zoom mode activated from four areas of the neo-SCJ including the area most suspicious for intestinal metaplasia (Figure 2 and 3). All procedures were performed by endoscopists with extensive experience in magnification endoscopy and Barrett's esophagus (JB and BW). After obtaining the images, each imaged area was biopsied precisely with two biopsies using a standard biopsy forceps.

**Histology**

All biopsy specimens were routinely processed, stained with hematoxylin-eosin, and evaluated. After routine assessment, all specimens were subsequently reviewed for the purpose of this study by one gastro-intestinal expert pathologist (FtK or MV) who was blinded to the endoscopic findings. The presence of intestinal metaplasia was defined as the presence of goblet cells in at least one biopsy specimen of the neo-SCJ (per patient) or in at least one biopsy specimen of an area (per area). In addition, presence of neoplasia was assessed according to the WHO classification.18

**Mucosal pattern classification**

The classification of the mucosal patterns was based on known literature and was developed and agreed upon consensus by researchers involved in the endoscopic imaging (JB, BW, LAH).12-15, 19, 20 The following patterns were defined: 1) “round” defined as small round pits of uniform size and shape regularly and orderly arranged; 2) “small tubular” defined as small tubuli without branching and a length <5x the width; 3) “large tubular” defined as large tubuli with or without branching and a length ≥5x the width; 4) “villous” defined a villiform appearance (Figure 1).
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Figure 2 Images of a patient with intestinal metaplasia in the neosquamocolumnar junction. Images of the neosquamocolumnar junction were first obtained in overview in the high resolution white light mode (A) and the NBI mode (B). The NBI overview image (B) shows where the areas are located of the subsequently obtained magnified still images in the NBI mode (C-F). Two areas (C&D) showed intestinal metaplasia on histology.

Assessors and image evaluation

Images were evaluated by four endoscopists with extensive experience with NBI and Barrett’s esophagus (WC, RB, MK and ES). All assessors were blinded to the pathology results.

The instructions and image evaluation were presented in PowerPoint (Windows 2003, Microsoft, USA) on an available computer. First, the assessors completed a standardized instruction explaining the aim of the study and the definition of the different mucosal patterns. Next, the assessors performed the image evaluation which was divided in two parts. In the first part the
over view images of the neo-SCJ were shown in random order. The high resolution white light and NBI overview image of the same patient were shown simultaneously, resulting in one slide per patient. In the second part, the NBI zoom images were shown in random order, resulting in one NBI zoom image of each area per slide. Assessors were not allowed to go back and forth in the presentation during the evaluation of the images.

The endoscopists scored each slide on a standardized case record form. Endoscopists scored the following items for the overview images (high resolution white light and NBI) of the neo-SCJ: 1) Quality of the image on a 10cm visual analogue scale (VAS); 2) Do you see Barrett's epithelium? (yes/no/unclear); 3) What helped you in deciding on the presence or absence of Barrett's epithelium? (high resolution white light image/NBI image/both/other); 4) Amount of “appreciated certainty” about the presence or absence of Barrett's epithelium on a 10cm VAS (0 defined as no clue at all and 10 defined as completely confident). For the zoom images endoscopists scored the following items: 1) Quality of the image on a 10cm VAS; 2) Which patterns do you see? ( “round”/“small tubular”/“large tubular”/“villous”/unclear, ≥1 options were allowed); 3) Do you think this area contains intestinal metaplasia? (yes/no/unclear); 4) Amount of “appreciated certainty” about the presence or absence of intestinal metaplasia on a 10cm VAS (0 defined as no clue at all and 10 defined as completely confident).

**Outcomes**

Primary outcomes of this study were:

1) Sensitivity and specificity for correct endoscopic identification of patients with intestinal metaplasia at the neo-SCJ based on the overview images.
   a. Defined as presence of Barrett's epithelium according to the assessor.

2) Sensitivity and specificity for correct endoscopic identification of patients with intestinal metaplasia in the neo-SCJ based on the combined assessment of the four zoom images.
   a. Defined as the presence of intestinal metaplasia according to the assessor in at least one of the four areas imaged in detail of the neo-SCJ.

Secondary outcomes were:

1) Sensitivity and specificity for correctly identifying neo-SCJ areas containing intestinal metaplasia based on the zoom images.
   a. Defined as the presence of intestinal metaplasia according to the assessor.
   b. Defined as the presence of “large tubular” and/or “villous” patterns according to the assessor.

2) Inter-observer agreement for “round”, “small tubular”, “large tubular” or “villous” patterns.

3) The influence of “appreciated certainty” of endoscopists on sensitivity and specificity.
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Figure 3 Images of a patient without intestinal metaplasia in the neosquamocolumnar junction. Images of the neosquamocolumnar junction were first obtained in overview in the high resolution white light mode (A) and the NBI mode (B). The NBI overview image (B) shows were the areas are located of the subsequently obtained magnified still images in the NBI mode (C-F). None of the four areas showed intestinal metaplasia on histology.

Statistical analysis

Statistical analysis was performed with the Statistical Software Package version 16.0.2 for windows (SPSS, Chicago, Illinois, USA). The evaluations of items scored as unclear (<4% of all assessments) were evaluated as missing data and excluded from the analysis.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated per patient and per area. Confidence intervals of these proportions were calculated with the Confidence Interval Analysis package.²¹
Inter-observer agreement was assessed with the multi-rater κ statistic via the SPSS mkappasc.sps macro (available at http://support.spss.com) and interpreted as a kappa value (0 poor agreement; 0.00 - 0.20 slight agreement; 0.21 - 0.40 fair agreement; 0.41 - 0.60 moderate agreement; 0.61 - 0.80 substantial agreement; 0.80 - 1.00 almost perfect agreement).  

Results

Baseline characteristics
A total of 21 patients were included with a neo-SCJ C≤1M≤1 after a mean of 2 (±1) RFA sessions. Patients had a mean age of 67 (±11) years and 78% was male. From these 21 patients, 21 overview high resolution white light and 21 overview NBI images were collected of the neo-SCJ; 83 NBI zoom images were obtained from 83 areas in the neo-SCJ (in 20 patients with 4 areas and in 1 patient with 3 areas). A histological diagnosis of intestinal metaplasia was present in 5 (24%) patients and in 11% of the neo-SCJ areas. Mean image quality on a 10cm VAS according to the four assessors was 7 (±2) for the overview images and 7 (±2) for the zoom images.

Per patient analysis
The sensitivity and specificity of the four endoscopists for identifying patients with intestinal metaplasia in the neo-SCJ based on the overview images or in at least one of the four zoom images of the neo-SCJ are shown in table 1. For the overview images, assessors indicated that their judgment of the presence or absence of Barrett’s epithelium was based on both images (high resolution white light and NBI) in 62% of the cases and on the NBI image alone in 32% of the cases. Mean “appreciated certainty” about the presence or absence Barrett’s epithelium on a 10cm VAS was 6(±2). In 15% of the cases, endoscopists scored the “appreciated certainty” with ≥9. Sensitivity and specificity were not significantly higher when endoscopists reported more “appreciated certainty” about their diagnosis (Table 2).
**Table 1** Accuracy for identifying intestinal metaplasia in the neosquamocolumnar junction by the endoscopists. Analyses per patient were made for the presence of Barrett’s epithelium and for the presence of intestinal metaplasia in at least one of the zoom images of the neosquamocolumnar junction as indicated by the endoscopists. Analyses per area were made for the presence of intestinal metaplasia and the type of mucosal pattern in a zoom image as indicated by the endoscopists.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
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<th>NPV</th>
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<td><strong>Per patient</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Presence Barrett’s epithelium in overview image</td>
<td>65% (95% CI 38-86%)</td>
<td>46% (95% CI 33-60%)</td>
<td>28% (95% CI 15-44%)</td>
<td>76% (95% CI 65-86%)</td>
<td>51% (95% CI 39-63%)</td>
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<td>Presence intestinal metaplasia in ≥1 of the 4 zoom images</td>
<td>95% (95% CI 75-100%)</td>
<td>5% (95% CI 1-13%)</td>
<td>24% (95% CI 15-35%)</td>
<td>75% (95% CI 19-99%)</td>
<td>26% (95% CI 17-37%)</td>
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<td><strong>Per area</strong></td>
<td></td>
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<tr>
<td>Presence intestinal metaplasia in zoom image</td>
<td>71% (95% CI 54-85%)</td>
<td>37% (95% CI 32-43%)</td>
<td>12% (95% CI 8-17%)</td>
<td>92% (95% CI 85-96%)</td>
<td>41% (95% CI 36-46%)</td>
</tr>
<tr>
<td>Presence of “large tubular” and/or “villous” patterns in zoom image</td>
<td>75% (95% CI 58-88%)</td>
<td>28% (95% CI 23-33%)</td>
<td>11% (95% CI 7-16%)</td>
<td>90% (95% CI 82-95%)</td>
<td>33% (95% CI 28-38%)</td>
</tr>
</tbody>
</table>

* 5/21 (24%) neo-SCJs contained intestinal metaplasia
* 11/83 (11%) areas contained intestinal metaplasia

CI confidence interval; PPV positive predictive value; NPV negative predictive value.
Table 2  Sensitivity and specificity for identifying intestinal metaplasia in the neosquamocolumnar junction by the endoscopists according to their “appreciated certainty” of the diagnosis scored on a 10 cm visual analogue scale (with 0 defined as no clue at all and 10 defined as completely confident).

<table>
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<tr>
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<th>“appreciated certainty” &lt;9</th>
<th>p-value*</th>
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<tr>
<td><strong>Per patient</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Presence Barrett’s epithelium in overview image</td>
<td>67% (95%CI 9-99%)</td>
<td>40% (95%CI 12-74%)</td>
<td>64% (95%CI 35-87%)</td>
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<tr>
<td><strong>Per area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence intestinal metaplasia in zoom image</td>
<td>71% (95%CI 29-96%)</td>
<td>26% (95%CI 16-40%)</td>
<td>71% (95%CI 51-87%)</td>
</tr>
</tbody>
</table>

* Fisher exact test
CI confidence interval
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Per neo-SCJ area analysis
The sensitivity and specificity of the four endoscopists for identifying intestinal metaplasia per neo-SCJ area are shown in table 1.

Mean “appreciated certainty” about the presence or absence of intestinal metaplasia on a 10cm VAS was 7(±2). In 19% of the cases endoscopists scored the “appreciated certainty” with ≥9. Again, sensitivity and specificity were not significantly higher when endoscopists reported more “appreciated certainty” about their diagnosis (Table 2).

According to the four assessors, “round”, “small tubular”, “large tubular” or “villous” patterns were observed in 5%, 44%, 45% and 36% of the areas, respectively. Mean kappa scores for “round”, “small tubular”, “large tubular” or “villous” patterns were 0.25 (95%CI 0-0.71), 0.09 (95%CI 0-0.18), 0.09 (95%CI 0-0.18) and 0.19 (95%CI 0.07-0.31), respectively.

Discussion
This study indicates that, endoscopic inspection of the neo-SCJ in overview using high resolution white light endoscopy and NBI as well as detailed inspection of the mucosal patterns with NBI can not reliably predict the presence of intestinal metaplasia at the neo-SCJ after RFA. In addition, inter-observer agreement for the different mucosal patterns seen with zoom NBI was found to be “slight” to “fair” and the patterns poorly correlated with the presence or absence of intestinal metaplasia. The presence of residual intestinal metaplasia at the neo-SCJ after RFA should therefore most likely be assessed by obtaining random biopsies immediately distal to the neo-SCJ.

In the per patient analysis using the evaluation of overview images we found 65% sensitivity and 46% specificity for the correct identification of patients with intestinal metaplasia in the neo-SCJ. This is in contrast to previous studies reporting a sensitivity of 92-94% and a specificity of 77% for the detection of patients with Barrett’s esophagus. These studies, however, included patients with clearly visible Barrett’s segments longer than 2cm, while our study included only patients a “normal” appearing neo-SCJ after RFA. The longer Barrett’s segments in combination with real time endoscopic evaluation (i.e. not blinded) of the overview aspect as well as the NBI zoom aspect of the Barrett’s segments may have biased the endoscopists in these studies. When we performed the analysis per patient with the four corresponding NBI zoom images of the neo-SCJ, sensitivity increased to 95%, specificity, however, dropped to an unacceptable 5%. This suggests that detailed inspection of the neo-SCJ with NBI does not provide useful information compared to inspection in overview.
When we analyzed zoom images of the neo-SCJ separately, the sensitivity for identifying areas with intestinal metaplasia (71-75%) was comparable to other studies in which the sensitivity ranged widely between 56% and 100%. The specificity was found to be less than other studies: 28-37% versus 79-95%. Then again, these evaluations were performed during real-time endoscopy and the majority also included a significant number of long Barrett's segments.

The relatively high sensitivity with low specificity in our study indicates that our endoscopists tended to overestimate the presence of intestinal metaplasia at the neo-SCJ. Several factors may have resulted in this overestimation. First, endoscopists were aware that the images were obtained from patients under RFA treatment for neoplastic Barrett's esophagus. Second, “large tubular” and/or “villous” patterns were the predominant patterns seen at the neo-SCJ. This raises the question whether these patterns are also predominantly present in normal patients at the SCJ, i.e., who never had Barrett's esophagus and have therefore not been treated with RFA, and whether these patterns are associated with intestinal metaplasia in these normal patients. Another reason for overestimation of intestinal metaplasia may be the wavy and not linear demarcation of the neo-SCJ. Endoscopists may interpret this wavy demarcation as remaining small tongues of Barrett's epithelium, while this wavy aspect of the neo-SCJ may be caused by neosquamous epithelium reaching into the cardia.

A higher level of “appreciated certainty” of the endoscopists about the presence or absence of Barrett's epithelium did not improve sensitivity or specificity. So even when endoscopists were highly confident about their diagnosis, their ability to correctly identify the patients and areas with and without intestinal metaplasia was not much better.

Inter-observer agreement between the four endoscopists was “fair” for the “round” and “villous” patterns and “slight” for the “small tubular” and “large tubular”. This low agreement reflects the arbitrariness in classifying the patterns uniformly despite that the assessors were endoscopists with extensive expertise with Barrett's esophagus and NBI zoom.

This study has some limitations that need to be addressed. First, this study was performed in an artificial population as patients were not consecutively included. Therefore, we were not able to assess the true rate of intestinal metaplasia in a normal appearing neo-SCJ after RFA. In addition, only a relatively small number of patients resulted to have intestinal metaplasia. Second, still images were used instead of video sequences. Video sequences or real-time endoscopy might allow a better interpretation of the neo-SCJ especially in overview. On the other hand, still images allow inspection of mucosal patterns without interfering movements and allow correct correlation to biopsy sampling. Finally, we can not exclude sampling error as only eight biopsies were obtained from the neo-SCJ for the evaluation of the overview images. The areas inspected in the zoom mode, however, were sampled by two biopsies which makes relevant sampling error unlikely.
Other endoscopic imaging techniques might be able to reliably detect intestinal metaplasia at the neo-SCJ after RFA. With endomicroscopy, goblet cells (i.e. intestinal metaplasia) are reported to be easy detectable. Drawbacks, however, are the fact that in order to reduce the sampling error a relatively large area needs to be inspected which can be time consuming. Also, performing endomicroscopy in the region of the neo-SCJ is difficult due to tangential imaging and respiratory movements. Moreover, no studies are available on the usefulness of endomicroscopy in detecting intestinal metaplasia at the neo-SCJ after RFA.

At this moment a reliable tool to detect residual intestinal metaplasia at the neo-SCJ after RFA is not available. How to decide when a patient needs additional RFA? In our opinion endoscopists should have a low threshold for performing focal RFA of the neo-SCJ. First, while balloon based RFA is a logical first step for ablation of circumferential Barrett's segments, the balloon makes relatively poor contact at the level of the gastric folds which makes it likely that intestinal metaplasia and neoplasia at this level are treated suboptimally. Second, recurrent neoplasia after endoscopic treatment of Barrett's neoplasia generally occurs at the level of the neo-SCJ. Finally, random biopsies of the neo-SCJ are inevitable associated with sampling error. As a result absence of intestinal metaplasia in random biopsies may be a false reassurance that the area has been affectively treated. We therefore perform additional RFA of a normal appearing neo-SCJ if the patient has not yet had a prior treatment with the focal RFA device of the complete neo-SCJ. In addition, the neo-SCJ is ablated circumferentially with focal RFA at all occasions when islands of columnar epithelium are detected proximal to the neo-SCJ since these can be considered unequivocal remnants of the former Barrett's segment. With this pragmatic approach our patients generally undergo at least two focal RFA ablations of the neo-SCJ. In case no islands are seen and the patient has undergone at least one circumferential treatment of the neo-SCJ with the focal RFA device, we obtain four random biopsies <5mm of the neo-SCJ generally with the endoscope in retroflexed position. When intestinal metaplasia is detected the patient is scheduled for an additional focal RFA of the whole neo-SCJ. When no intestinal metaplasia is found the patient is considered to have been effectively treated and is followed-up at six and twelve months and annually thereafter. If during follow-up intestinal metaplasia is detected in a normal appearing neo-SCJ we do not consider this an indication for treatment. Additional treatment is reserved for rare cases were neoplasia is detected at this level.

In conclusion, endoscopic inspection of the neo-SCJ with high resolution white light and NBI in overview or by detailed inspection of the mucosal patterns with NBI zoom endoscopy does not reliably predict completeness of eradication of intestinal metaplasia after RFA. The presence of residual intestinal metaplasia in the cardia after RFA should therefore be assessed by random biopsies taken immediately distal to the neo-SCJ.
References


