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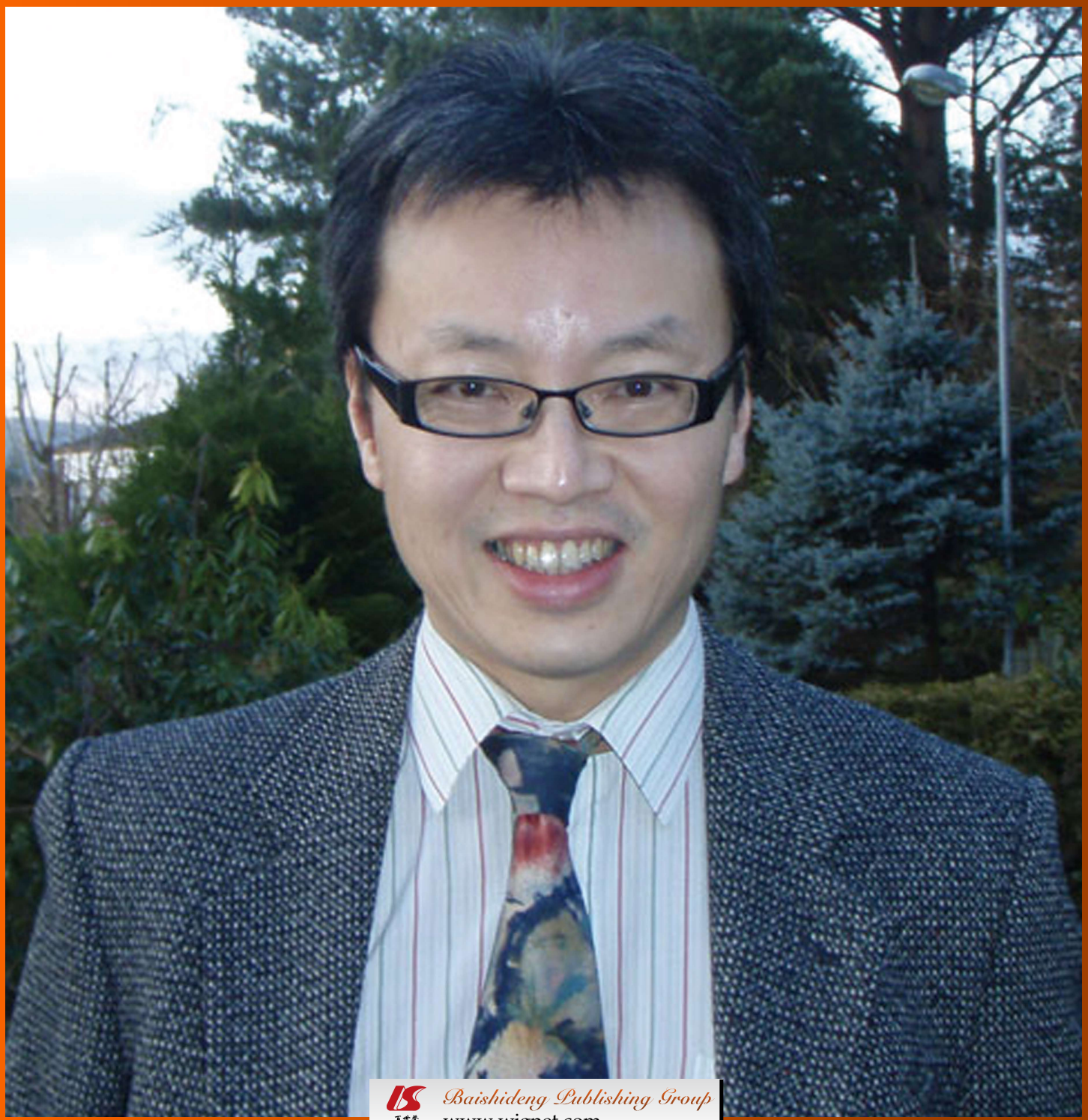

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MINIREVIEWS

Narrow band imaging with magnification for the diagnosis of lesions in the upper gastrointestinal tract

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Abstract

Endoscopy plays an important role in the diagnosis and management of gastrointestinal (GI) tract disorders. Chromoendoscopy has proven to be superior to white light endoscopy for early detection of various GI lesions. This has however been fraught with problems. The use of color stains, time taken to achieve an effect and the learning curve associated with the technique has been some of the pitfalls. Narrow band imaging (NBI) particularly in combination with magnifying endoscopy may allow the endoscopist to accomplish a fairly accurate diagnosis with good histological correlation similar to results achieved with chromoendoscopy. Such enhanced detection of pre-malignant and early neoplastic lesions in the gastrointestinal tract should allow better targeting of biopsies and could ultimately prove to be cost effective. Various studies have been done demonstrating the utility of this novel technology. This article will review the impact of NBI in the diagnosis of upper gastrointestinal tract disorders.

Key words: Narrow band imaging; Magnifying endoscopy; Upper gastrointestinal tract

Core tip: Narrow band imaging with magnifying endoscopy has shown promising results in improving detection and characterization of gastrointestinal lesions. This may allow better targeting of biopsies, improved prediction of histology, appropriate treatment and better patient outcomes. Most studies have been conducted in expert centers and carried out only by one or a few observers. Large-scale prospective multi center randomized trials are needed to duplicate the results achieved in these institutions.

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INTRODUCTION

Recent advances in endoscopic imaging technologies have enabled endoscopists to improve the capability of detecting and characterizing lesions in gastrointestinal tract (GIT). Amongst some of these novel technologies, narrow band imaging (NBI) appears to be the most promising. Current available data on the utility of NBI with magnification (NBI-ME) has been encouraging for Barrett's esophagus, early Oropharyngeal, esophageal and gastric cancers and to a lesser extent reflux disease and gastritis. It also has a role in aiding endoscopic resection where margin assessment is essential. This review will focus on the role of NBI-ME in the diagnosis of lesions in upper gastrointestinal tract.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

NBI enables detailed observation of the microvascu-

lature in the esophageal mucosa, described as intraepithelial papillary capillary loops (IPCL's). The NBI-ME findings of early squamous cell carcinoma (SCC) include a well-demarcated brownish area, elevated margins, loss of visible branching vessels and a type Ⅳ or type V intraepithelial papillary capillary loops pattern[1,2]. Inoue originally described intraepithelial papillary capillary loops into 4 distinct entities: dilation, meandering, caliber changes and difference in shapes[3,4]. Type Ⅳ intraepithelial papillary capillary loops shows 2 or 3 of the four patterns, whilst Type V intraepithelial papillary capillary loops demonstrates all 4 characteristic changes. Type Ⅲ intraepithelial papillary capillary loops (minimal proliferation or meandering in a brownish area) is considered borderline or low grade intra-epithelial neoplasia. Thus, a follow up endoscopy is generally recommended for these patients. However, type Ⅱ intraepithelial papillary capillary loops (enlarged but linear and regular vessels) indicates regenerative tissue or inflamed mucosa. Type I intraepithelial papillary capillary loops, are generally normal vessels with smooth, slender, regular caliber with a smaller diameter (10 μm).

Muto *et al*[5] conducted a multicentre randomised controlled trial on 320 patients with a history of Squamous Cell CA (SCC), comparing white light endoscopy (WLE) with NBI in the detection of Squamous Cell CA in patients with a history of head and neck Squamous Cell CA or previous esophageal Squamous Cell CA. The sensitivity of NBI for a diagnosis of superficial cancer was 100% for the oropharynx and 97.2% for the esophagus. The diagnostic accuracy was 90% when two endoscopic criteria, namely, a well demarcated brownish area and an irregular micro vascular pattern, were used.

Goda *et al*[6] conducted a non-randomized comparative study of 101 lesions of esophageal Squamous Cell CA, which gauged the sensitivity and specificity of WLE, NBI and endoscopic ultrasound (EUS) in predicting the depth of superficial esophageal Squamous Cell CA. The authors concluded that all 3 modalities did not differ significantly. Kuraoka *et al*[7] conducted a study comparing endoscopy with iodine staining to NBI. Endoscopy assisted with NBI was more useful in the detection of early esophageal Squamous Cell CA than that obtained with iodine. Another study assessed the efficacy of 1204 high-resolution esophagoscopies with NBI using a novel "Endo View" Program. Color segmentation of narrow band images apparently increased the chances of diagnosing even the smallest abnormality in the esophagus. NBI endoscopy also allowed specifying premalignant lesions in esophageal mucosa in both low grade and high-grade dysplasia (HGD)[8].

A consensus of expert endoscopists from the Asia-Pacific region put all of this together and reported a strong agreement on importance of interpretation of both vascular architecture and surface structure of the superficial mucosa in the esophagus. NBI was useful for detection of esophageal Squamous Cell CA (100% consensus achieved), distinguishing neoplastic from non-neoplastic lesions (89% consensus), determining the extent of the neoplasia (78% consensus) and depth of the tumor (100% consensus). However, the panel of experts agreed that chromo endoscopy is still superior to delineate the extent of the tumor[9]. They also agreed that there was no significant difference in terms of sensitivity and specificity for the assessment of the depth of tumor invasion by NBI when compared to EUS.

BARRETT'S ESOPHAGUS

Singh *et al*[10] conducted a study on 109 patients with more than 1000 corresponding biopsies, which not only validated a simplified classification of the various morphologic patterns visualized in Barrett's Esophagus (BE) and corresponding histology with high predictive values, but also confirmed its reproducibility and repeatability when the grading system was used by both endoscopists experienced in the use of NBI and those unfamiliar with it. On the basis of the 1021 areas visualized, NBI-ME allowed correct prediction of 99% of the areas harboring intestinal metaplasia (IM) and 96% of the areas demonstrating high grade dysplasia (HGD). However intestinal metaplasia was not clearly differentiated from low grade dysplastic lesions. Mannath *et al*[11] in a large meta analysis found a very high sensitivity and specificity of NBI in diagnosing in high grade dysplasia patients with Barrett's Esophagus.

GASTRO-ESOPHAGEAL REFLUX DISEASE AND NON-EROSIVE REFLUX DISEASE

Approximately 60% of patients with gastro-esophageal reflux disease (GERD) have normal standard endoscopy and are labeled as suffering from non-erosive reflux disease (NERD)[12]. NBI-ME can detect microvascular changes and also enhance the contrast between esophageal and gastric mucosa[13]. Microvascular changes of non-erosive reflux disease on NBI include increased number and dilatation of intraepithelial papillary capillary giving an inverted fir tree appearance, punctate erythema, loss of vascular palisade pattern and triangular indentation of squamo-columnar junction above the Z line[14]. Changes below the Z line include islands of squamous epithelium and increased vascular markings[15,16]. Some of these features were tested in a study comparing ten control subjects and eleven patients with non-erosive reflux disease confirmed by a validated questionnaire, standard endoscopy and 24-h pH-metry[17]. The investigators proposed and explored seven different distal esophageal mucosal appearances that can be observed with a high-resolution endoscope (triangular lesions, apical mucosal breaks, palisade vessels, pin point vessels, branching vessels, villiform mucosa and serrated squamo-columnar junction). However none of these changes proved to be sufficiently sensitive and specific to justify their use as a diagnostic criterion for non-erosive reflux disease. A study conducted by Fock *et al*[18] concluded that NBI detected a significantly higher prevalence of

micro-erosions (gastro-esophageal reflux disease 100%, non-erosive reflux disease 52.8% and controls 23%) and increased vascularity (gastro-esophageal reflux disease 95%, non-erosive reflux disease 91.7% and controls 36.7%) but a lower prevalence of round pit patterns (gastro-esophageal reflux disease 4.9%, non-erosive reflux disease 5.6% and controls 70%).

Tseng *et al*[15] studied 82 patients where 20 were detected as having gastro-esophageal reflux disease by WLE. Out of the remaining 62 patients declared normal by WLE, NBI detected an additional 44 patients having erosions. They also demonstrated that the changes which visualized on NBI could predict a therapeutic response in patients with gastro-esophageal reflux disease. Sharma *et al*[14] compared NBI with WLE in a prospective study of 101 patients. Patients with and without gastro-esophageal reflux disease symptoms were examined by standard WLE followed by NBI. The features seen only by NBI were compared between gastro-esophageal reflux disease patients and controls. A significantly higher proportion of patients with gastro-esophageal reflux disease had increased number (OR = 12.6), dilatation (OR = 20), tortuosity of intraepithelial papillary capillary (OR = 6.9) and increased vascularity at the squamo-columnar junction (OR = 9.3) compared with controls.

GASTRITIS AND *HELICOBACTER PYLORI*

Helicobacter pylori (*H. pylori*) is the commonest cause of chronic gastritis[19]. This can lead to intestinal metaplasia and dysplasia; conditions which may progress onto gastric carcinoma[20]. On NBI-ME, the normal gastric corpus and fundus have small round pits, sub-epithelial capillaries networks (SECN) in a honeycomb pattern and stellate shaped collecting venules (CV) arranged at regular intervals in deeper mucosa[21,22]. These patterns have a 100% predictive value for normal corporal mucosa[23]. The normal gastric antrum has a reticular pattern of circular pits and coiled elongated sub-epithelial capillaries networks. The collecting venules are situated too deep to be visible[21,24]. *H. pylori* gastritis visualized by NBI shows a loss of collecting venules due to associated inflammation and this pattern has 100% sensitivity, 92% specificity and a positive predictive value (PPV) of 100% for *H. pylori* gastritis. *H. pylori* related atrophic gastritis is patchy starting from Incisura and progressively involves the Antrum, body and corpus. NBI findings suggestive of atrophy are loss of pits and sub-epithelial capillaries networks. The sensitivity and specificity of these findings for atrophic gastritis have been suggested to be up to 90% or above[23].

Dalal *et al*[25] conducted a pilot study in the stomach that concluded that when compared to WLE, abnormal findings on NBI had a sensitivity of 100% and a specificity of 90.6%; whereas WLE has a sensitivity of only 42.9% and specificity of 75%. Negative predictive value (NPV) of NBI was 100%, whereas WLE has Negative predictive value of 85.7%. However, with a small-sized study of 25 patients, further refinement and validation of the NBI grading criteria was suggested. Banerjee and colleagues also compared NBI with WLE on 74 patients and showed that high resolution endoscopy with NBI could be a potential tool for the instantaneous real time diagnosis of *H. pylori* infection. The sensitivity, specificity, positive predictive value and negative predictive value for absence of infection were 85%, 93%, 96% and 77% respectively[26].

SUPERFICIAL GASTRIC CANCER

As with all cancers, an early diagnosis is crucial for a good prognosis in gastric carcinoma, which is the second leading cause of cancer related deaths worldwide[27-31]. Atrophy, metaplasia, dysplasia followed by neoplasia are the usual sequence of events[32,33] in some of these patients. NBI may assist in identifying premalignant lesions and hence enable appropriate therapy. Amorphous pit pattern, irregular size and/or arrangement of pits or complete loss of pits along with abnormal micro-vascular pattern are associated with neoplastic lesions. Regular, round, slit or villous like pits indicate non-neoplastic lesions[34-36]. These changes are however not always straightforward as findings can be altered by many conditions such as chronic inflammation, ulceration, atrophy or metaplasia and *H. pylori* infection[37-39]. Superficial but elevated lesions make the visibility of micro-vascular pattern difficult[35,40,41].

A consensus of expert endoscopists in the Asia-Pacific region agreed that NBI is not useful for detection of gastric carcinoma at an early stage. They however concurred that NBI increases sensitivity and accuracy of differential diagnosis of early gastric carcinoma (EGC) in elevated, flat and depressed lesions. NBI may also distinguish tumor margins from the surrounding normal mucosa. They also agreed that NBI has no significant role in detecting tumor depths as the narrow band of light is speculated to penetrate to only 200-250 μm into the superficial mucosa[9]. Approximately 40% of early gastric carcinoma are of the undifferentiated type according to Japanese literature[42,43]. This type of early gastric carcinoma can extend subepithelially and may be covered by non-neoplastic foveolar epithelium. In undifferentiated early gastric carcinoma, it is recommended that biopsies are obtained from the surrounding mucosa to diagnose the undetectable tumor extent[44].

Light blue crest (LBC) is a fine, blue-white line on the crest of the epithelial surface/gyri. An JK conducted a study on 42 patients and concluded that the Light blue crest sign (LBC) observed in the gastric mucosa with magnifying NBI endoscopy are highly accurate indicators of the presence of Intestinal Metaplasia (IM) and Light blue crest also correlates with progression to severe Intestinal Metaplasia. For the diagnosis of Intestinal Metaplasia, Light blue crest had a sensitivity, specificity, and accuracy of 72.1%, 96.0%, and 84.9%[45]. Uedo *et al*[46] tested NBI-ME on 34 patients with atrophic gastritis and demonstrated that the appearance of Light blue crest correlated

with histological evidence of Intestinal Metaplasia, with a sensitivity of 89% (95%CI: 83-96), a specificity of 93% (95%CI: 88-97), a positive predictive value of 91% (95%CI: 85-96), a negative predictive value of 92% (95%CI: 87-97) and an accuracy of 91% (95%CI: 88-95). Yao *et al*[47] reported that the hallmark of a white opaque substance (WOS) is the presence of lipid droplets (LDs) that accumulate in the superficial part of the epithelial neoplasia within the stomach. The authors also reported that the white opaque substance in adenomas was regular and homogeneous, whereas the white opaque substance in adenocarcinomas was irregular and speckled. Ueyama *et al*[48] suggested that the white opaque substance-positive epithelium corresponded to the dysplasia in this lesion. The presence of a white opaque substance in a gastric hyperplasia may be considered an endoscopic finding that is predictive of the neoplastic transformation of a gastric hyperplasia. Therefore, in gastric hyperplasia, white opaque substance positivity may be considered an endoscopic finding that indicates endoscopic resection[48].

CELIAC DISEASE

Normal duodenal mucosa exhibits regularly arranged finger like villi and a regular network of capillaries on high resolution magnifying WLE[49]. Reduced duodenal folds, scalloping of fold margins, mosaic pattern of mucosa and grooves in the mucosa are usual conventional endoscopic signs for celiac disease[50-54]. However these findings are not reliable in patchy[55,56] or milder cases of subtotal atrophy[57]. Overall, the sensitivity, specificity, positive predictive value and negative predictive value for villous atrophy on NBI are 100%, 91%, 83% and 100% respectively[58].

Banerjee *et al*[59] mentioned earlier in 2008 that NBI may be a useful yet simple adjunctive tool for the direct visualization of villous architecture and guide to tissue sampling. This may improve the diagnostic yield as well as reduce the number of biopsy specimens that need to be taken. Singh *et al*[60] conducted a study using NBI-ME to detect villous atrophy in patients presenting with suspected celiac disease using forty-one videos obtained from 21 patients (3 celiac disease, 18 normal). The overall sensitivity and specificity in correctly distinguishing the presence or absence of villi were 93% and 98% respectively, with inter-observer and intra-observer agreement (kappa, κ) at 0.82 and 0.86 respectively. The sensitivity and specificity in differentiating partial from total villous atrophy were 83.3% and 100% respectively, with κ at 0.73 and 0.68 respectively.

CONCLUSION

Narrow band imaging is a promising endoscopic technology which may improve the diagnostic accuracy of detecting and characterizing premalignant and neoplastic lesions in the upper gastrointestinal tract. Most studies have been conducted in expert centers and carried out by one or a few observers. Large-scale prospective multicenter randomized trials are needed to duplicate the results achieved in these institutions. Standardization of endoscopic criteria and amalgamation of the various classifications cannot be overemphasized. Once this is achieved, teaching and learning modules for more widespread dissemination to the community will be crucial.

REFERENCES

1 **Muto M**, Katada C, Sano Y, Yoshida S. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. *Clin Gastroenterol Hepatol* 2005; **3**: S16-S20 [PMID: 16012987 DOI: 10.1016/S1542-3565(05)00262-4]

2 **Muto M**, Nakane M, Katada C, Sano Y, Ohtsu A, Esumi H, Ebihara S, Yoshida S. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. *Cancer* 2004; **101**: 1375-1381 [PMID: 15368325 DOI: 10.1002/cncr.20482]

3 **Inoue H**, Honda T, Nagai K, Kawano T, Yoshino K, Takeshita K, Endo M. Ultra-high magnification endoscopic observation of carcinoma in situ. *Dig Endosc* 1997; 9: 16-18 [DOI: 10.1111/j.1443-1661.1997.tb00453.x]

4 **Inoue H**. [Endoscopic diagnosis of tissue atypism (EA) in the pharyngeal and esophageal squamous epithelium; IPCL pattern classification and ECA classification]. *Kyobu Geka* 2007; **60**: 768-775 [PMID: 17763682]

5 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. 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 [PMID: 20177025 DOI: 10.1200/JCO.2009.25.4680]

6 **Goda K**, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, Sumiyama K, Imazu H, Matsuda K, Kaise M, Kato T, Omar S. Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma. *Dis Esophagus* 2009; **22**: 453-460 [PMID: 19222533 DOI: 10.1111/j.1442-2050.2009.00942.x]

7 **Kuraoka K**, Hoshino E, Tsuchida T, Fujisaki J, Takahashi H, Fujita R. Early esophageal cancer can be detected by screening endoscopy assisted with narrow-band imaging (NBI). *Hepatogastroenterology* 2009; **56**: 63-66 [PMID: 19453030]

8 **Yao K**, Iwashita A, Tanabe H, Nishimata N, Nagahama T, Maki S, Takaki Y, Hirai F, Hisabe T, Nishimura T, Matsui T. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. *Gastrointest Endosc* 2008; **68**: 574-580 [PMID: 18656862 DOI: 10.1016/j.gie.2008.04.011]

9 **Uedo N**, Fujishiro M, Goda K, Hirasawa D, Kawahara Y, Lee JH, Miyahara R, Morita Y, Singh R, Takeuchi M, Wang S, Yao T. Role of narrow band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia-Pacific region. *Dig Endosc* 2011; **23** Suppl 1: 58-71 [PMID: 21535204 DOI: 10.1111/j.1443-1661.2011.01119.x]

10 **Singh R**, Anagnostopoulos GK, Yao K, Karageorgiou H, Fortun PJ, Shonde A, Garsed K, Kaye PV, Hawkey CJ, Ragunath K. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. *Endoscopy* 2008; **40**: 457-463 [PMID: 18459090 DOI: 10.1055/s-2007-995741]

11 **Mannath J**, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Endoscopy* 2010; **42**: 351-359 [PMID: 20200809 DOI: 10.1055/s-0029-1243949]

12 **Hershcovici T**, Fass R. Nonerosive Reflux Disease (NERD) - An Update. *J Neurogastroenterol Motil* 2010; **16**: 8-21 [PMID: 20535321 DOI: 10.5056/jnm.2010.16.1.8]

13 **Fock KM**, Teo EK, Chan Y, Law N, Chua T, Tan J, Poh C, Kwek A, Lu S. The utility of narrow band imaging (NBI) endoscopy in the detection of Goblet metaplasia in patients with gastroesophageal reflux disease (GORD). *Gastrointestinal Endoscopy* 2006; **63**: AB109 [DOI: 10.1016/j.gie.2006.03.129]

14 **Sharma P**, Wani S, Bansal A, Hall S, Puli S, Mathur S, Rastogi A. A feasibility trial of narrow band imaging endoscopy in patients with gastroesophageal reflux disease. *Gastroenterology* 2007; **133**: 454-464; quiz 674 [PMID: 17681166 DOI: 10.1053/j.gastro.2007.06.006]

15 **Tseng PH**, Chen CC, Chiu HM, Liao WC, Wu MS, Lin JT, Lee YC, Wang HP. Performance of narrow band imaging and magnification endoscopy in the prediction of therapeutic response in patients with gastroesophageal reflux disease. *J Clin Gastroenterol* 2011; **45**: 501-506 [PMID: 20733514 DOI: 10.1097/MCG.0b013e3181eeb115]

16 **Lee YC**, Lin JT, Chiu HM, Liao WC, Chen CC, Tu CH, Tai CM, Chiang TH, Chiu YH, Wu MS, Wang HP. Intraobserver and interobserver consistency for grading esophagitis with narrow-band imaging. *Gastrointest Endosc* 2007; **66**: 230-236 [PMID: 17643694 DOI: 10.1016/j.gie.2006.10.056]

17 **Edebo A**, Tam W, Bruno M, Van Berkel AM, Jönson C, Schoeman M, Tytgat G, Dent J, Lundell L. Magnification endoscopy for diagnosis of nonerosive reflux disease: a proposal of diagnostic criteria and critical analysis of observer variability. *Endoscopy* 2007; **39**: 195-201 [PMID: 17236126 DOI: 10.1055/s-2006-945112]

18 **Fock KM**, Teo EK, Ang TL, Tan JY, Law NM. The utility of narrow band imaging in improving the endoscopic diagnosis of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2009; **7**: 54-59 [PMID: 18852068 DOI: 10.1016/j.cgh.2008.08.030]

19 **McColl KE**. Clinical practice. Helicobacter pylori infection. *N Engl J Med* 2010; **362**: 1597-1604 [PMID: 20427808 DOI: 10.1056/NEJMcp1001110]

20 **Peek RM**, Fiske C, Wilson KT. Role of innate immunity in Helicobacter pylori-induced gastric malignancy. *Physiol Rev* 2010; **90**: 831-858 [PMID: 20664074 DOI: 10.1152/physrev.00039.2009]

21 **Yao K**, Oishi T. Microgastroscopic findings of mucosal microvascular architecture as visualized by magnifying endoscopy. *Gastrointest Endosc* 2001; **13**: S27-S33 [DOI: 10.1111/j.1443-1661.2001.00114.x]

22 **Yagi K**, Nakamura A, Sekine A. Characteristic endoscopic and magnified endoscopic findings in the normal stomach without Helicobacter pylori infection. *J Gastroenterol Hepatol* 2002; **17**: 39-45 [PMID: 11895551 DOI: 10.1046/j.1440-1746.2002.02665.x]

23 **Anagnostopoulos GK**, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, Foley S, Sunil S, Atherton JJ, Hawkey C, Ragunath K. High-resolution magnification endoscopy can reliably identify normal gastric mucosa, Helicobacter pylori-associated gastritis, and gastric atrophy. *Endoscopy* 2007; **39**: 202-207 [PMID: 17273960 DOI: 10.1055/s-2006-945056]

24 **Yao K**. Gastric microvascular architecture as visualized by magnifying endoscopy: body and antral mucosa without pathologic change demonstrate two different patterns of microvascular architecture. *Gastrointest Endosc* 2004; **59**: 596-597; author reply 597 [PMID: 15044912 DOI: 10.1016/S0016-5107(03)02825-6]

25 **Dalal K**, Zhang XF, Gonzalez-Haba Ruiz M, Westerhoff M, Reddy KG, Hart J, Konda VJ. Sa1721 Conventional narrow band imaging for the improved detection of gastritis. *Gastrointestinal Endoscopy* 2012; 75: AB254 [DOI: 10.1016/j.gie.2012.04.241]

26 **Banerjee R**, Ramji C, Mansard MJ, Shekharan A, Darisetty S, Tandan M, Rao GV, Reddy DN. High resolution narrow band imaging (NBI) can identify normal gastric mucosa and H. Pylori (HP) associated gastritis. *Gastrointestinal Endoscopy* 2007; 65: AB178 [DOI: 10.1016/j.gie.2007.03.314]

27 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]

28 **Oliveira FJ**, Ferrão H, Furtado E, Batista H, Conceição L. Early gastric cancer: Report of 58 cases. *Gastric Cancer* 1998; **1**: 51-56 [PMID: 11957043 DOI: 10.1007/s101200050054]

29 **Pisani P**, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. *Int J Cancer* 1993; **55**: 891-903 [PMID: 8253525 DOI: 10.1002/ijc.2910550604]

30 **Parkin DM**, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001; **37** Suppl 8: S4-66 [PMID: 11602373 DOI: 10.1016/S0959-8049(01)00267-2]

31 **Parkin DM**. International variation. *Oncogene* 2004; **23**: 6329-6340 [PMID: 15322508 DOI: 10.1038/sj.onc.1207726]

32 **Lansdown M**, Quirke P, Dixon MF, Axon AT, Johnston D. High grade dysplasia of the gastric mucosa: a marker for gastric carcinoma. *Gut* 1990; **31**: 977-983 [PMID: 2210465 DOI: 10.1136/gut.31.9.977]

33 **Di Gregorio C**, Morandi P, Fante R, De Gaetani C. Gastric dysplasia. A follow-up study. *Am J Gastroenterol* 1993; **88**: 1714-1719 [PMID: 8213713]

34 **Yao K**, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; **41**: 462-467 [PMID: 19418401 DOI: 10.1055/s-0029-1214594]

35 **Tsuji Y**, Ohata K, Sekiguchi M, Ohno A, Ito T, Chiba H, Gunji T, Fukushima J, Yamamichi N, Fujishiro M, Matsuhashi N, Koike K. Magnifying endoscopy with narrow-band imaging helps determine the management of gastric adenomas. *Gastric Cancer* 2012; **15**: 414-418 [PMID: 22252155 DOI: 10.1007/s10120-011-0133-2]

36 **Miwa K**, Doyama H, Ito R, Nakanishi H, Hirano K, Inagaki S, Tominaga K, Yoshida N, Takemura K, Yamada S, Kaneko Y, Katayanagi K, Kurumaya H, Okada T, Yamagishi M. Can magnifying endoscopy with narrow band imaging be useful for low grade adenomas in preoperative biopsy specimens? *Gastric Cancer* 2012; **15**: 170-178 [PMID: 22407064 DOI: 10.1007/s10120-011-0093-6]

37 **Nonaka K**, Arai S, Ban S, Kitada H, Namoto M, Nagata K, Ochiai Y, Togawa O, Nakao M, Nishimura M, Ishikawa K, Sasaki Y, Kita H. Prospective study of the evaluation of the usefulness of tumor typing by narrow band imaging for the differential diagnosis of gastric adenoma and well-differentiated adenocarcinoma. *Dig Endosc* 2011; **23**: 146-152 [PMID: 21429020 DOI: 10.1111/j.1443-1661.2010.01070.x]

38 **Nakamura M**, Shibata T, Tahara T, Yoshioka D, Okubo M, Mizoguchi Y, Kuroda M, Arisawa T, Hirata I. The usefulness of magnifying endoscopy with narrow-band imaging to distinguish carcinoma in flat elevated lesions in the stomach diagnosed as adenoma by using biopsy samples. *Gastrointest Endosc* 2010; **71**: 1070-1075 [PMID: 20438898 DOI: 10.1016/j.gie.2009.12.032]

39 **Omori T**, Kamiya Y, Tahara T, Shibata T, Nakamura M, Yonemura J, Okubo M, Yoshioka D, Ishizuka T, Maruyama N, Kamano T, Fujita H, Nakagawa Y, Nagasaka M, Iwata M, Arisawa T, Hirata I. Correlation between magnifying narrow band imaging and histopathology in gastric protruding/or polypoid lesions: a pilot feasibility trial. *BMC Gastroenterol* 2012; **12**: 17 [PMID: 22356674 DOI: 10.1186/1471-230X-12-17]

40 **Yao K**. How is the VS (vessel plus surface) classification system applicable to magnifying narrow-band imaging examinations of gastric neoplasias initially diagnosed as low-grade adenomas? *Gastric Cancer* 2012; **15**: 118-120 [PMID: 22407063 DOI: 10.1007/s10120-011-0132-3]

41 **Yao K**. The endoscopic diagnosis of early gastric cancer. *Ann Gastroenterol* 2013; 26

42 **Nakamura K**, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gann* 1968; **59**: 251-258 [PMID: 5726267]

43 **Sugano H**, Nakamura K, Kato Y. Pathological studies of human gastric cancer. *Acta Pathol Jpn* 1982; **32** Suppl 2: 329-347 [PMID: 6765003]

44 **Everett SM**, Axon AT. Early gastric cancer in Europe. *Gut*

1997; **41**: 142-150 [PMID: 9301490 DOI: 10.1136/gut.41.2.142]
45 **An JK**, Song GA, Kim GH, Park do Y, Shin NR, Lee BE, Woo HY, Ryu DY, Kim DU, Heo J. Marginal turbid band and light blue crest, signs observed in magnifying narrow-band imaging endoscopy, are indicative of gastric intestinal metaplasia. *BMC Gastroenterol* 2012; **12**: 169 [PMID: 23185997 DOI: 10.1186/1471-230X-12-169]
46 **Uedo N**, Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T, Imanaka K, Takeuchi Y, Higashino K, Ishiguro S, Tatsuta M. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006; **38**: 819-824 [PMID: 17001572 DOI: 10.1055/s-2006-944632]
47 **Yao K**, Iwashita A, Nambu M, Tanabe H, Nagahama T, Maki S, Ishikawa H, Matsui T, Enjoji M. Nature of white opaque substance in gastric epithelial neoplasia as visualized by magnifying endoscopy with narrow-band imaging. *Dig Endosc* 2012; **24**: 419-425 [PMID: 23078433 DOI: 10.1111/j.1443-1661.2012.01314.x]
48 **Ueyama H**, Matsumoto K, Nagahara A, Gushima R, Hayashi T, Yao T, Watanabe S. A white opaque substance-positive gastric hyperplastic polyp with dysplasia. *World J Gastroenterol* 2013; **19**: 4262-4266 [PMID: 23864793 DOI: 10.3748/wjg.v19.i26.4262]
49 **Cammarota G**, Martino A, Pirozzi GA, Cianci R, Cremonini F, Zuccalà G, Cuoco L, Ojetti V, Montalto M, Vecchio FM, Gasbarrini A, Gasbarrini G. Direct visualization of intestinal villi by high-resolution magnifying upper endoscopy: a validation study. *Gastrointest Endosc* 2004; **60**: 732-738 [PMID: 15557949 DOI: 10.1016/S0016-5107(04)02170-4]
50 **McIntyre AS**, Ng DP, Smith JA, Amoah J, Long RG. The endoscopic appearance of duodenal folds is predictive of untreated adult celiac disease. *Gastrointest Endosc* 1992; **38**: 148-151 [PMID: 1568611 DOI: 10.1016/S0016-5107(92)70380-0]
51 **Brocchi E**, Corazza GR, Caletti G, Treggiari EA, Barbara L, Gasbarrini G. Endoscopic demonstration of loss of duodenal folds in the diagnosis of celiac disease. *N Engl J Med* 1988; **319**: 741-744 [PMID: 3412397 DOI: 10.1056/NEJM198809223191202]
52 **Jabbari M**, Wild G, Goresky CA, Daly DS, Lough JO, Cleland DP, Kinnear DG. Scalloped valvulae conniventes: an endoscopic marker of celiac sprue. *Gastroenterology* 1988; **95**: 1518-1522 [PMID: 3181676]
53 **Stevens FM**, McCarthy CF. The endoscopic demonstration of coeliac disease. *Endoscopy* 1976; **8**: 177-180 [PMID: 1026384 DOI: 10.1055/s-0028-1098406]
54 **Smith AD**, Graham I, Rose JD. A prospective endoscopic study of scalloped folds and grooves in the mucosa of the duodenum as signs of villous atrophy. *Gastrointest Endosc* 1998; **47**: 461-465 [PMID: 9647369 DOI: 10.1016/S0016-5107(98)70245-7]
55 **Achkar E**, Carey WD, Petras R, Sivak MV, Revta R. Comparison of suction capsule and endoscopic biopsy of small bowel mucosa. *Gastrointest Endosc* 1986; **32**: 278-281 [PMID: 3743980 DOI: 10.1016/S0016-5107(86)71846-4]
56 **Dickey W**, Hughes D. Prevalence of celiac disease and its endoscopic markers among patients having routine upper gastrointestinal endoscopy. *Am J Gastroenterol* 1999; **94**: 2182-2186 [PMID: 10445547 DOI: 10.1111/j.1572-0241.1999.01348.x]
57 **Dickey W**, Hughes D. Disappointing sensitivity of endoscopic markers for villous atrophy in a high-risk population: implications for celiac disease diagnosis during routine endoscopy. *Am J Gastroenterol* 2001; **96**: 2126-2128 [PMID: 11467643 DOI: 10.1111/j.1572-0241.2001.03947.x]
58 **Cammarota G**, Pirozzi GA, Martino A, Zuccalà G, Cianci R, Cuoco L, Ojetti V, Landriscina M, Montalto M, Vecchio FM, Gasbarrini G, Gasbarrini A. Reliability of the "immersion technique" during routine upper endoscopy for detection of abnormalities of duodenal villi in patients with dyspepsia. *Gastrointest Endosc* 2004; **60**: 223-228 [PMID: 15278049 DOI: 10.1016/S0016-5107(04)01553-6]
59 **Banerjee R**, Reddy DN. High-resolution narrow-band imaging can identify patchy atrophy in celiac disease: targeted biopsy can increase diagnostic yield. *Gastrointest Endosc* 2009; **69**: 984-985 [PMID: 19327498 DOI: 10.1016/j.gie.2008.07.012]
60 **Singh R**, Nind G, Tucker G, Nguyen N, Holloway R, Bate J, Shetti M, George B, Tam W. Narrow-band imaging in the evaluation of villous morphology: a feasibility study assessing a simplified classification and observer agreement. *Endoscopy* 2010; **42**: 889-894 [PMID: 21072704 DOI: 10.1055/s-0030-1255708]

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BRIEF ARTICLE

Endoscopic mucosal resection of Barrett's esophagus detects high prevalence of subsquamous intestinal metaplasia

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Abstract

AIM: To report the prevalence of Subsquamous intestinal metaplasia (SSIM) in patients undergoing endoscopic mucosal resection (EMR) for staging of Barrett's esophagus (BE).

METHODS: Thirty-three patients with BE associated neoplasia underwent EMR at our institution between September 2009 and September 2011; 22 of these patients met study inclusion criteria. EMR was targeted at focal abnormalities within the BE segment. EMR was performed in standardized fashion using a cap-assisted band ligation technique, and resection specimens were assessed for the presence of SSIM. Demographic and clinical data were analyzed to determine predictors of SSIM.

RESULTS: SSIM was detected in 59% of patients. SSIM was detected in 73% of patients with short segment (< 3 cm) BE, and in 45% of patients with long-segment (≥ 3 cm) BE (P = NS). There was no association between presence/absence of SSIM and age, gender, or stage of BE-associated neoplasia.

CONCLUSION: EMR detects SSIM in a majority of patients with BE-associated neoplasia. While the long-term clinical significance of SSIM remains uncertain, these results highlight the importance of EMR as an optimal diagnostic tool for staging of BE and detection of SSIM, and should further limit concerns that SSIM is purely a post-ablation phenomenon.

Key words: Barrett esophagus; Barrett epithelium; Endoscopy; Esophageal cancer; Pathology

Core tip: Subsquamous intestinal metaplasia (SSIM) is the term used to describe glandular Barrett's tissue which is buried beneath overlying squamous mucosa and not visible endoscopically. Esophageal forceps which fail to contain lamina propria are of insufficient depth to assess for the presence of SSIM. This study of patients with Barrett's esophagus (BE) undergoing endoscopic mucosal resection, previously naïve to endoscopic therapy, detected SSIM in 59% of patients. These findings demonstrate that SSIM is a common occurrence in the natural history of BE, and should limit concerns that SSIM is purely a post-ablation phenonomenon.

Yachimski P, Shi C, Slaughter JC, Washington MK. Endoscopic mucosal resection of Barrett's esophagus detects high prevalence of subsquamous intestinal metaplasia. *World J Gastrointest Endosc* 2013; 5(12): 590-594 Available from: URL: http://www.

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INTRODUCTION

Barrett's esophagus (BE) is defined as intestinal metaplasia of the esophageal mucosa, and is recognized as the major known risk factor for esophageal adenocarcinoma[1]. Criteria for the diagnosis of BE have typically included the presence of endoscopically visible mucosal changes proximal to the gastroesophageal junction, with histopathology demonstrating columnar epithelium with goblet cells. The concept of subsquamous intestinal metaplasia (SSIM), often referred to as "buried Barrett's", challenges these criteria by implying that metaplastic, glandular BE tissue beneath intact surface squamous mucosa may not be endoscopically apparent, and may be detectable only by histopathologic analysis of mucosal tissue specimens containing lamina propria. A theoretical concern is that SSIM may harbor neoplastic tissue which eludes standard endoscopic surveillance.

SSIM has been reported in BE patients who have received long-term pharmacologic acid suppression therapy[2], and both before and after endoscopic therapy in cohorts across a range of endoscopic ablation modalities including photodynamic therapy (PDT)[3] and radiofrequency ablation (RFA)[4,5]. Estimates of the prevalence of SSIM have varied widely across studies, with a recent systematic review indicating a prevalence ranging between 0 and 28%[6]. This variability may in part reflect inconsistencies in biopsy technique and depth across studies.

The majority of prior studies reporting the prevalence of SSIM have been based on mucosal specimens obtained by forceps biopsy, with the high-end estimate (28%) originating from a study of endoscopic mucosal resection (EMR). EMR, frequently employed for staging of BE-associated neoplasia, offers both a greater depth and surface area of tissue acquisition when compared with forceps biopsies, and therefore may have a higher yield for detection of SSIM. Our hypothesis was that prior reports have underestimated the prevalence of SSIM, and the aim of this study was to determine the prevalence of SSIM in patients undergoing EMR for staging of BE.

MATERIALS AND METHODS

Approval to conduct this retrospective study was granted by the Vanderbilt University Institutional Review Board. A database query was performed to identify patients with BE who had undergone EMR between September 2009 and September 2011. Clinical and endoscopic data were extracted from the electronic medical record.

Endoscopic evaluations were performed by a single endoscopist (PY). Candidates for EMR included patients referred for staging of BE-associated neoplasia, with prior biopsies documenting the presence of low-grade dysplasia (LGD), high-grade dysplasia (HGD), and/or adenocarcinoma within the BE segment. EMR is performed as previously described[7]. EMR are performed with a cap-assisted device (Duette Multi-Band Mucosectomy, Cook Medical, Limerick, Ireland). Resections are completed using a snare at a blended current setting (ERBE VIO 200-S electrosurgical unit, set to snare hot biopsy mode with coag effect 1 and maximum Watts 20). If necessary, piecemeal EMR is repeated until the target area has been resected.

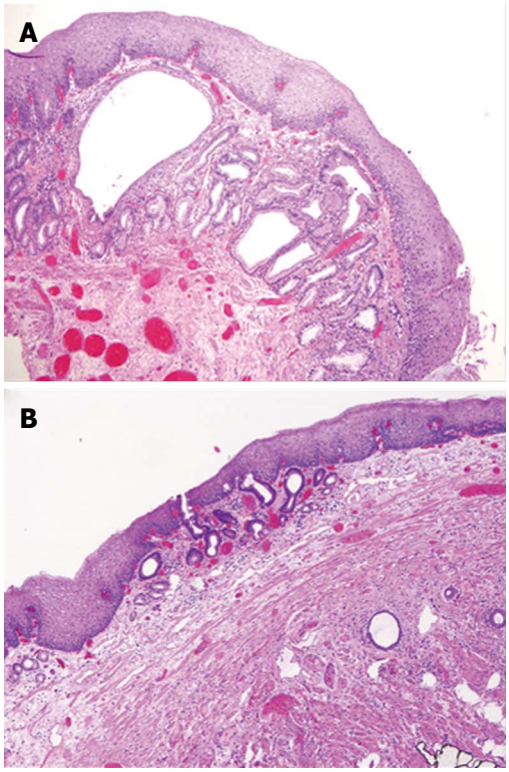

Figure 1 Esophageal endoscopic mucosal resection specimens demonstrating two morphologic subtypes of subsquamous intestinal metaplasia. A: Subsquamous intestinal metaplasia (SSIM) with no direct extension to the mucosa; B: SSIM penetrating through the overlying squamous epithelium and onto the luminal surface.

The pathology laboratory is notified of specimen submission, and specimens are sectioned in order to preserve tissue orientation and architecture. Formalin-fixed and paraffin-embedded specimens are reviewed by two expert gastrointestinal pathologists (CS and MKW) as previously described[7]. In cases of dysplasia, dysplasia is graded as LGD or HGD. For adenocarcinoma, a local stage is assigned (pT1a, pT1b, *etc.*) according to American Joint Committee on Cancer 7th edition staging manual.

For the purposes of this study, the presence of SSIM was assessed in each EMR specimen. SSIM was defined as glandular intestinal metaplasia within the lamina propria and without apparent continuity with surface BE. Two morphologic subtypes were identified: (1) SSIM with no direct extension to the mucosa (Figure 1A); and (2) SSIM with glands penetrating through the overlying squamous epithelium and onto the luminal surface, surrounded completely by squamous epithelium (Figure 1B).

Exclusion criteria were: (1) prior endoscopic or surgical therapy for BE; (2) the presence of invasive carcinoma detected by histopathologic analysis of the EMR speci-

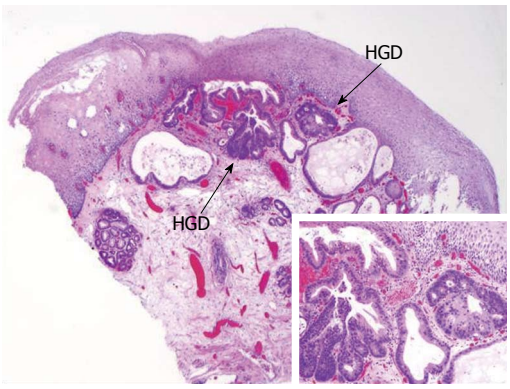

Figure 2 Esophageal endoscopic mucosal resection specimens demonstrating subsquamous intestinal metaplasia with high-grade dysplasia. HGD: High-grade dysplasia.

men; and (3) the absence of squamous mucosa in the EMR specimen. With respect to the last exclusion criteria, by definition squamous mucosa must be present in the resected in specimen in order to assess for SSIM. Therefore, only EMR specimens obtained in proximity to the endoscopically visible squamocolumnar junction and including squamous tissue were eligible for analysis. EMR specimens obtained entirely from within a BE segment and not containing squamous mucosa were therefore not included.

Descriptive and univariate statistical analysis was performed using the R statistics program. A two-sided $P < 0.05$ was considered significant.

RESULTS

Thirty-three patients underwent EMR during the study time period. One patient who had undergone radiofrequency ablation prior to EMR and one patient who had undergone prior surgical esophagectomy were excluded. Five patients were excluded due to the absence of squamous tissue in the EMR specimen. An additional four patients were found to have invasive cancer (T1b or greater) and were excluded on this basis. Therefore, the final cohort consisted of 22 subjects. These 22 patients underwent a total of 26 EMR sessions (mean sessions 1.2 per patient, range 1-2). Eighty-two percent of subjects were male, and the mean age of subjects was 64 (range 41-80) years. Mean maximum BE length among the subjects was 3.8 (range 0-12) cm. Pre-EMR histopathologic diagnosis, based on forceps biopsies, was LGD in 5% (1/22), HGD in 41% (9/22), intramucosal (T1a) adenocarcinoma in 36% (8/22), and invasive adenocarcinoma in 18% (4/22) of subjects, respectively.

SSIM was detected in EMR specimens in 59% (13/22) of patients. SSIM was detected in 73% (8/11) of patients with short segment (< 3 cm length) BE and 45% (5/11) of patients with long segment (≥ 3 cm length) BE (P = NS). There was no association between presence/absence of SSIM and age or gender. There was no association between presence/absence of SSIM and stage of neoplasia.

Of the 13 cases with SSIM, 3 (23%) contained high-grade dysplasia in SSIM (Figure 2). Four patients underwent two EMR sessions separated in each case by 2-3 mo intervals, and SSIM was present in the index EMR specimen in each of these patients. Adverse events of EMR were limited to esophageal stricture requiring endoscopic dilation in 5% (1/22) of patients; bleeding requiring endoscopic therapy, hospital admission and packed red blood cell transfusion in one patient; delayed bleeding requiring endoscopic evaluation but no endoscopic therapy and no transfusion in one patient; and aspiration requiring hospital admission in one patient.

DISCUSSION

This study demonstrates that SSIM is present in the majority of patients undergoing EMR for staging of BE-associated neoplasia. The prevalence of SSIM in this cohort (59%) is considerably higher than previously reported from tissue-based analysis. Prior studies have reported prevalence of SSIM ranging between 0 and 28%[6]. The majority of these studies were based on results of forceps biopsies, which may underestimate prevalence of SSIM due to inadequate sampling of the lamina propria. A 28% prevalence rate of SSIM, often detected at or just proximal to the squamocolumnar junction, was reported in a prior study with EMR as the tissue sampling method[8]. Our findings approach the high SSIM prevalence rate (73%) detected by optical coherence tomography imaging in a recently reported study[9].

Our protocol consisted of focal EMR targeted at specific lesions within the BE segment. Single-session resection is confined to less than 50% of the mural circumference, in order to limit the risk of post-EMR stricture. These focal EMRs do not resect the entirety of the squamocolumnar junction, as might be achieved with a widefield EMR or endoscopic submucosal dissection technique-therefore, it is likely that our study underestimates the true prevalence of SSIM in the cohort.

This study features a systematic, regimented approach to the staging of BE-associated neoplasia, which includes close collaboration between an endoscopist trained in BE endotherapy and expert gastrointestinal pathologists, and which we believe facilitates detection of SSIM. EMR specimens were obtained and evaluated according to set protocol, which included use of specific electrocautery settings. Electrocautery settings for esophageal EMR are not standardized across practices, and may vary by endoscopist and institution, including use of "cut" versus "coag" application for resection and variations in this regard may influence the degree of thermal injury and artifact at lateral resection margins including squamous mucosa, potentially influencing the ability to detect SSIM in proximity to these margins.

This study is limited by its small size and retrospective nature, which limits the ability to assess predictors of SSIM. Details of prior duration of exposure to pharmacologic gastric acid suppression and extent of prior endoscopic biopsy surveillance of BE, both factors which can promote ingrowth of squamous islands within BE, are not available. The study also does not include control groups, for instance to assess the prevalence of SSIM in

patients with BE staged by forceps biopsy alone or the prevalence of SSIM in BE patients without neoplasia. The results of this study may not be generalizable to patients with BE without dysplasia or carcinoma.

The long-term clinical significance of SSIM remains a topic of uncertainty, particularly with respect to patients who have undergone endotherapy for BE. Cases of dysplasia and adenocarcinoma arising from SSIM have been reported following treatment of BE-associated neoplasia with PDT[10,11] and argon plasma coagulation[12]. A recent systematic review tallied a total of 34 reported cases of neoplasia (ranging from LGD to invasive adenocarcinoma) arising within SSIM following BE endotherapy[6]. In some cases when neoplasia is present and involving both surface and subsquamous structures, however, it may be difficult to precisely and definitively implicate a subsquamous origin of neoplasia. In follow-up of patients treated in a randomized study of PDT, among patients with biopsies demonstrating recurrence of neoplasia, the highest grade of dysplasia/cancer was always present in surface epithelium and not contained solely in SSIM[3].

On the other hand, SSIM is phenotypically distinct from surface BE on a molecular level. For instance, SSIM following PDT has low Ki-67 crypt proliferation rates and lower rates of aneuploidy when compared with pre-treatment BE[13]. Additional alterations in biomarker expression in SSIM may be a consequence of relative protection from exposure to mutagenic gastric and bile acid reflux[14]. In this regard, SSIM may in theory have a lower malignant potential than surface BE.

While the current study is not informative regarding the long-term malignant potential of SSIM, it does fundamentally alter estimates of the native prevalence of SSIM in an endotherapy-naïve cohort. This creates a critical context for the emerging role of widespread endotherapy for BE, as we aim to understand how endotherapy alters the prevalence and natural history of SSIM. Estimates of SSIM prevalence following BE endotherapy have varied widely, both within and across ablation modalities. Among a randomized study of patients treated with PDT, the prevalence of SSIM was reported to increase from 5.8% pre-treatment to 30% at 5-years post-treatment[3]. In the AIM-Dysplasia trial, a randomized study of RFA plus proton pump inhibitor versus proton pump inhibitor alone, the prevalence of SSIM in the RFA arm was 25.2% pre-treatment, 5.1% at 12 mo post-treatment, and 3.8% at 24 mo post-treatment[4,5]. A prospective study of RFA for treatment of nondysplastic BE, however, reported no SSIM in any of 1473 biopsy specimens from 50 subjects at 5 years post-treatment[15].

An important variable which may influence the ability to identify SSIM, detectable only in specimens containing lamina propria structures, is biopsy depth following BE endotherapy. A recent study reported that lamina propria is present in fewer than 40% of biopsy specimens obtained from neosquamous esophageal epithelium following BE endotherapy[16]. Given this significant limitation, the optimal comparison would be comparison of SSIM in EMR specimens pre-therapy and EMR specimens of neosquamous epithelium post-therapy. A high-volume European center reported no SSIM in EMR specimens from 14 patients following RFA or combined EMR/RFA therapy for BE[17].

Yet EMR is not likely to be acceptable for routine post-treatment surveillance of BE. As the current study demonstrates, although EMR is well-tolerated by the majority of patients, there is a limited but real risk of adverse events including bleeding and esophageal stricture formation. The potential need for improved means of detection and surveillance of SSIM may present an opportunity for endoscopic imaging modalities currently in development and capable of detailed intraluminal imaging of subsurface esophageal structures, including optical coherence tomography or optical frequency domain imaging[9,18-20]. Ultimately, a full understanding of the clinical importance of SSIM will be achievable only through future study of SSIM in tissue specimens obtained from BE patients longitudinally at multiple time points during the course of disease[21].

In summary, this study demonstrates that EMR detects SSIM in a majority of patients with BE-associated neoplasia. This finding should further dampen concerns that SSIM is a post-ablation phenomenon, and may fundamentally alter our understanding of the natural history of BE. As EMR becomes an increasingly important and widely utilized tool in the staging and therapy of BE, further attention to the detection and reporting of SSIM is necessary in order to define the clinical significance of this variant of intestinal metaplasia.

COMMENTS

Background

Barrett's esophagus (BE) refers to intestinal metaplasia of the esophageal mucosa, and is the principal risk factor for esophageal adenocarcinoma. BE has a characteristic salmon-colored appearance and is typically readily visible on endoscopic inspection. Subsquamous intestinal metaplasia (SSIM) is the term used to describe BE tissue which is buried beneath overlying squamous mucosa and not visible endoscopically. Esophageal neoplasia arising from SSIM has been reported. As the use of endoscopic ablation therapies for BE has grown, there are concerns that ablation will accelerate development of SSIM and lead to risk of neoplasia which is invisible or elusive to standard endoscopic surveillance.

Research frontiers

There are limited data regarding the prevalence and natural history of SSIM, particularly among BE patients who have not previously undergone endoscopic treatment. Esophageal biopsies may underestimate the prevalence of SSIM due to limited depth of biopsy samples. The aim of this study was to assess the prevalence of BE among patients undergoing endoscopic mucosal resection, an endoscopic technique which allows for removal of a tissue sample of much greater surface area and depth compared to a forceps biopsy

Innovations and breakthroughs

This is the highest reported prevalence of SSIM in patients with BE naïve to endoscopic therapy.

Applications

The finding of a high prevalence of SSIM among patients with BE may alter the authors' understanding of the natural history of BE, and provide an opportunity for new technologies capable of imaging subepithelial structures to play a role in endoscopic surveillance of BE.

Terminology

Endoscopic mucosal resection (EMR), is an esophageal tissue resection technique which has important diagnostic and therapeutic value in the endoscopic management of Barrett's esophagus neoplasia. Subsquamous intestinal metaplasia (SSIM), informally referred to as "buried Barrett's", is the term used to describe glandular esophageal epithelium which is buried beneath overlying

squamous mucosa and not visible endoscopically.

Peer review

In his study, Dr. Linsdell provides a review of the physiological, biophysical and pharmacological relevance of a class of inhibitors of the CFTR channel, *i.e.*, the ones that directly block Cl movements across the open pore. The author has to be congratulated for this excellent work. The review is clear, well organised and written, and with effective figures. It will be an interesting reading also for non-experts in the field.

REFERENCES

1 **Falk GW**. Barrett's esophagus. *Gastroenterology* 2002; **122**: 1569-1591 [PMID: 12016424 DOI: 10.1053/gast.2002.33427]

2 **Sharma P**, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Squamous islands in Barrett's esophagus: what lies underneath? *Am J Gastroenterol* 1998; **93**: 332-335 [PMID: 9517634]

3 **Bronner MP**, Overholt BF, Taylor SL, Haggitt RC, Wang KK, Burdick JS, Lightdale CJ, Kimmey M, Nava HR, Sivak MV, Nishioka N, Barr H, Canto MI, Marcon N, Pedrosa M, Grace M, Depot M. Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2009; **136**: 56-64; quiz 351-2 [PMID: 18996379 DOI: 10.1053/j.gastro.2008.10.012]

4 **Shaheen NJ**, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; **360**: 2277-2288 [PMID: 19474425 DOI: 10.1056/NEJMoa0808145]

5 **Shaheen NJ**, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, Sharma VK, Eisen GM, Fennerty MB, Hunter JG, Bronner MP, Goldblum JR, Bennett AE, Mashimo H, Rothstein RI, Gordon SR, Edmundowicz SA, Madanick RD, Peery AF, Muthusamy VR, Chang KJ, Kimmey MB, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Dumot JA, Falk GW, Galanko JA, Jobe BA, Hawes RH, Hoffman BJ, Sharma P, Chak A, Lightdale CJ. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology* 2011; **141**: 460-468 [PMID: 21679712 DOI: 10.1053/j.gastro.2011.04.061]

6 **Gray NA**, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2011; **106**: 1899-908; quiz 1909 [PMID: 21826111 DOI: 10.1038/ajg.2011.255]

7 **Ayers K**, Shi C, Washington K, Yachimski P. Expert pathology review and endoscopic mucosal resection alters the diagnosis of patients referred to undergo therapy for Barrett's esophagus. *Surg Endosc* 2013; **27**: 2836-2840 [PMID: 23389078 DOI: 10.1007/s00464-013-2830-x]

8 **Chennat J**, Ross AS, Konda VJ, Lin S, Noffsinger A, Hart J, Waxman I. Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: implications for surveillance and endotherapy management. *Gastrointest Endosc* 2009; **70**: 417-421 [PMID: 19555948 DOI: 10.1016/j.gie.2009.01.047]

9 **Zhou C**, Tsai TH, Lee HC, Kirtane T, Figueiredo M, Tao YK, Ahsen OO, Adler DC, Schmitt JM, Huang Q, Fujimoto JG, Mashimo H. Characterization of buried glands before and after radiofrequency ablation by using 3-dimensional optical coherence tomography (with videos). *Gastrointest Endosc* 2012; **76**: 32-40 [PMID: 22482920 DOI: 10.1016/j.gie.2012.02.003]

10 **Mino-Kenudson M**, Ban S, Ohana M, Puricelli W, Deshpande V, Shimizu M, Nishioka NS, Lauwers GY. Buried dysplasia and early adenocarcinoma arising in barrett esophagus after porfimer-photodynamic therapy. *Am J Surg Pathol* 2007; **31**: 403-409 [PMID: 17325482]

11 **Overholt BF**, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. *Gastrointest Endosc* 2003; **58**: 183-188 [PMID: 12872083]

12 **Van Laethem JL**, Peny MO, Salmon I, Cremer M, Devière J. Intramucosal adenocarcinoma arising under squamous re-epithelialisation of Barrett's oesophagus. *Gut* 2000; **46**: 574-577 [PMID: 10716690]

13 **Hornick JL**, Mino-Kenudson M, Lauwers GY, Liu W, Goyal R, Odze RD. Buried Barrett's epithelium following photodynamic therapy shows reduced crypt proliferation and absence of DNA content abnormalities. *Am J Gastroenterol* 2008; **103**: 38-47 [PMID: 18076737]

14 **Odze RD**, Lauwers GY. Histopathology of Barrett's esophagus after ablation and endoscopic mucosal resection therapy. *Endoscopy* 2008; **40**: 1008-1015 [PMID: 19065484 DOI: 10.1055/s-0028-1103416]

15 **Fleischer DE**, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R, Chang KJ, Muthasamy R, Lightdale CJ, Santiago N, Pleskow DK, Dean PJ, Wang KK. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* 2010; **42**: 781-789 [PMID: 20857372]

16 **Gupta N**, Mathur SC, Dumot JA, Singh V, Gaddam S, Wani SB, Bansal A, Rastogi A, Goldblum JR, Sharma P. Adequacy of esophageal squamous mucosa specimens obtained during endoscopy: are standard biopsies sufficient for postablation surveillance in Barrett's esophagus? *Gastrointest Endosc* 2012; **75**: 11-18 [PMID: 21907985 DOI: 10.1016/j.gie.2011.06.040]

17 **Pouw RE**, Gondrie JJ, Rygiel AM, Sondermeijer CM, ten Kate FJ, Odze RD, Vieth M, Krishnadath KK, Bergman JJ. Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia. *Am J Gastroenterol* 2009; **104**: 1366-1373 [PMID: 19491850 DOI: 10.1038/ajg.2009.88]

18 **Mori Y**, Itoh Y, Tajima N. Angiotensin II receptor blockers downsize adipocytes in spontaneously type 2 diabetic rats with visceral fat obesity. *Am J Hypertens* 2007; **20**: 431-436 [PMID: 17386352]

19 **Suter MJ**, Vakoc BJ, Yachimski PS, Shishkov M, Lauwers GY, Mino-Kenudson M, Bouma BE, Nishioka NS, Tearney GJ. Comprehensive microscopy of the esophagus in human patients with optical frequency domain imaging. *Gastrointest Endosc* 2008; **68**: 745-753 [PMID: 18926183 DOI: 10.1016/j.gie.2008.05.014]

20 **Adler DC**, Zhou C, Tsai TH, Lee HC, Becker L, Schmitt JM, Huang Q, Fujimoto JG, Mashimo H. Three-dimensional optical coherence tomography of Barrett's esophagus and buried glands beneath neosquamous epithelium following radiofrequency ablation. *Endoscopy* 2009; **41**: 773-776 [PMID: 19746317 DOI: 10.1055/s-0029-1215045]

21 **Yachimski P**, Falk GW. Subsquamous intestinal metaplasia: implications for endoscopic management of Barrett's esophagus. *Clin Gastroenterol Hepatol* 2012; **10**: 220-224 [PMID: 22020059 DOI: 10.1016/j.cgh.2011.10.009]

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BRIEF ARTICLE

Finding the solution for incomplete small bowel capsule endoscopy

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Abstract

AIM: To evaluate whether the use of real time viewer (RTV) and administration of domperidone to patients with delayed gastric passage of the capsule could reduce the rate of incomplete examinations (IE) and improve the diagnostic yield of small bowel capsule endoscopy (SBCE).

METHODS: Prospective single center interventional study, from June 2012 to February 2013. Capsule location was systematically checked one hour after ingestion using RTV. If it remained in the stomach, the patient received 10 mg domperidone per os and the location of the capsule was rechecked after 30 min. If the capsule remained in the stomach a second dose of 10 mg of domperidone was administered orally. After another 30 min the position was rechecked and if the capsule remained in the stomach, it was passed into the duodenum by upper gastrointestinal (GI) endoscopy. The rate of IE and diagnostic yield of SBCE were compared with those of examinations performed before the use of RTV or domperidone in our Department (control group, January 2009 - May 2012).

RESULTS: Both groups were similar regarding age, sex, indication, inpatient status and surgical history. The control group included 307 patients, with 48 (15.6%) IE. The RTV group included 82 patients, with 3 (3.7%) IE, $P = 0.003$. In the control group, average gastric time was significantly longer in patients with IE than in patients with complete examination of the small bowel (77 min *vs* 26 min, $P = 0.003$). In the RTV group, the capsule remained in the stomach one hour after ingestion in 14/82 patients (17.0%) *vs* 48/307 (15.6%) in the control group, $P = 0.736$. Domperidone did not significantly affect small bowel transit time (260 min *vs* 297 min, $P = 0.229$). The capsule detected positive findings in 39% of patients in the control group and 49% in the RTV group ($P = 0.081$).

CONCLUSION: The use of RTV and selective administration of domperidone to patients with delayed gastric passage of the capsule significantly reduces incomplete examinations, with no effect on small bowel transit time or diagnostic yield.

Key words: Small bowel capsule endoscopy; Prokinetic drugs; Domperidone; Incomplete examination

Core tip: Incomplete small bowel capsule endoscopy (SBCE) is an important limitation of the technique and may occur in up to 20% of patients. Delayed gastric passage of the capsule is a major factor leading to incomplete SBCE. Selective administration of oral dom-

peridone to patients with delayed gastric passage of the capsule assessed with the real time viewer (RTV) effectively reduces the rate of incomplete SBCE. The administration of domperidone does not influence small bowel transit time of the capsule. There is an overall trend towards higher diagnostic yield of SBCE when domperidone is selectively administered. The use of the RTV should be adopted systematically in patients undergoing small bowel capsule endoscopy.

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INTRODUCTION

Small bowel capsule endoscopy (SBCE) was introduced in clinical practice in 2001, and it proved to be a valuable non-invasive technique to examine the small-bowel[1]. SBCE may be useful in a wide range of clinical settings, such as obscure gastrointestinal (GI) bleeding[2], suspected and known Crohn's disease (CD)[3-5], celiac disease[6] and polyposis syndromes[7], with a higher diagnostic yield when compared to conventional diagnostic techniques[2,4,8-11]. An important limitation of SBCE is the possibility of incomplete examination of the small-bowel, which occurs when the capsule does not reach the cecum within the recording time of approximately 9 h. The rate of IE is approximately 20% to 30% in most studies[12,13]. In such cases, the value of SBCE is limited by the fact that it may miss lesions located in the distal segments of the small bowel, eventually leading to the need for further examinations and increased costs[14]. Retrospective studies identified some factors that may be associated with incomplete small-bowel SBCE examination, such as inpatient status[14], previous abdominal surgery[14] and prolonged gastric transit time (GTT)[14,15], while the effect of age or medical conditions such as diabetes mellitus remains controversial[16]. Currently, there is no consensus regarding the use of prokinetic drugs in SBCE to reduce the rate of IE with SBCE[17]. In theory, prokinetics might be useful by improving gastric emptying, but their routine use in patients submitted to SBCE is not widely established[17]. Randomized prospective studies failed to demonstrate an improvement in SBCE completion rates with the use of metoclopramide, administered before the procedure[18,19]. One of the recent advances in the field of SBCE is the availability of a portable external viewer for direct monitoring of the images received during the procedure. The new Given® Data Recorder (DR3) with the real time viewer (RTV) enables real-time viewing during SBCE procedure (Figure 1). The European Society of Gastrointestinal Endoscopy (ESGE) recommended that patients at increased risk for IE might benefit from the use of the RTV peri-procedurally, with subsequent endoscopic placement of the capsule in the duodenum when indicated[20]. The aim of our study was to assess whether the prokinetic agent domperidone, in association with the RTV, could reduce the rate of IE and improve the diagnostic yield of SBCE.

MATERIALS AND METHODS

We conducted a single center prospective interventional study, comparing the use of domperidone in association with RTV in consecutive patients undergoing SBCE from June 2012 to February 2013 (RTV group) *vs* a control group of patients who had been submitted to SBCE following the standard procedure with no use of RTV or domperidone, from January 2009 to May 2012, in our Department. The RTV images were viewed by gastroenterologists with a large experience in SBCE to check the capsule position during the procedure. The RTV was used to confirm the passage of the capsule to the small-bowel one hour after ingestion. If the capsule remained in the stomach, 10 mg of domperidone were administered *per os* and the location of the capsule was rechecked after 30 min. If it still remained in the stomach, an additional dose of 10 mg of domperidone was administered orally and after another 30 min the location of the capsule was rechecked; then if still in the stomach the capsule was placed directly in the duodenum by upper endoscopy using a basket. All patients followed a 24 h clear liquid diet and 12 h fasting prior to SBCE (PillCam® SB2, Given® Imaging Ltd. Yoqneam, Israel), and were advised not to eat for 4 h after swallowing the capsule. No oral purge was administered. Patients with obstructive symptoms, known small bowel strictures and/or in whom some bowel purge or prokinetics were used did not enter the study. One experienced gastroenterologist, with more than 100 SBCE procedures, reviewed SBCE images using RAPID Reader® (Given® Diagnostic Imaging System, Given® Imaging). The completion rate was defined as the frequency of SBCE reaching the cecum within the battery life (approximately 9 h). Gastric transit time (GTT) was recorded from the first gastric image to the first duodenum image, and small-bowel transit time (SBTT) was recorded from the first duodenum image to the first cecal image, or alternatively the last image of the small bowel if the capsule did not reach the cecum within recording time.

Statistical analysis

Continuous variables were expressed as mean ± SD and analyzed with the unpaired *t*-test. Fisher's exact test was used to compare incomplete examinations rate and diagnostic yield between the two groups. A *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS® (version 17.0 for Windows®, SPSS inc®, Chicago, IL, USA). All patients gave their informed consent prior to their inclusion in

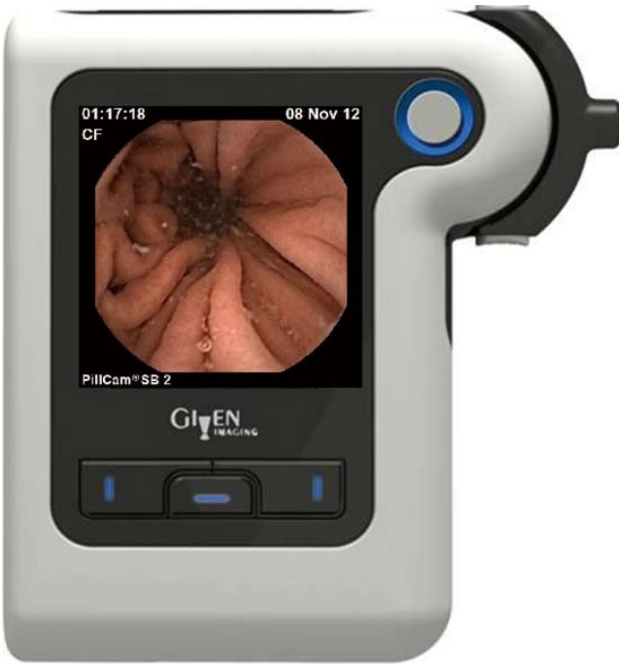

Figure 1 Real time viewer detecting the capsule inside the stomach more than one hour after ingestion.

the study.

RESULTS

A total of 84 consecutive SBCE were performed after the introduction of RTV in our Department. Two procedures were excluded because the capsule was *ad initium* passed into the duodenum under endoscopic assistance using the AdvanCE® delivery system. In the control group, a total of 359 SBCE were retrospectively reviewed. Forty procedures were excluded because patients had received bowel preparation with polyethylene glycol prior to SBCE in the setting of a clinical trial[21], and another 12 patients were excluded because the capsule was immediately passed into the duodenum under endoscopic assistance using the AdvanCE® system, due to swallowing disorders or previous gastric surgery. Thus, a total of 82 patients using the RTV and 307 matched controls were included in the study analysis. The baseline clinical characteristics and indications for SBCE in both groups are summarized in Table 1. Variables such as age, gender, previous abdominal surgery, inpatient status and indication for SBCE were not significantly different between the two groups. The rate of IE was 15.6% (n = 48) in the control group *vs* 3.7% (n = 3) in the RTV group (P = 0.003). In the RTV group, domperidone was administered in 14/82 patients (17.0%), in whom the capsule remained in the stomach 1 h after ingestion, while in the control group the proportion of patients with the capsule remaining in the stomach 1 h after ingestion was 48/307 (15.6%), P = 0.736. In the control group, average gastric time was significantly longer in patients with IE than in patients with complete examination of the small bowel (77 min *vs* 26 min, P = 0.003). In the RTV group, no differences were observed in the SBTT among patients who received or did not receive domperidone (260 min *vs* 297 min, P = 0.229). In one patient (7.0%) out of the 14 patients in the RTV group in whom domperidone was administered, the capsule remained in the stomach two hours after ingestion, and an upper endoscopy was performed to deliver the capsule to the duodenum using a basket. SBCE positive findings were observed in 39% of the control group *vs* 49% of the RTV group (P = 0.081). None of the 14 patients who received domperidone had any side effect related to the drug.

DISCUSSION

SBCE emerged as a valuable non-invasive diagnostic technique to investigate the entire small-bowel. However, a major drawback is the rate of incomplete examinations, reaching up to 20% to 30%[12,13]. Some conditions have been associated with incomplete small bowel examination, such as inpatient status[14] or previous abdominal surgery[14], while the effect of age or medical conditions such as diabetes mellitus remain controversial[16]. Importantly, delayed GTT has been consistently reported as a leading cause of incomplete small bowel examination[14,15]. Our study supports the hypothesis that the systematic use of the RTV included in the new Given® Data Recorder (DR3), in association with domperidone to overcome delayed gastric transit in selected cases, enhancesthe completion rate of SBCE. Domperidone is a type Ⅱ dopamine antagonist similar to metoclopramide, with similar effects on gastric emptying but with lower central side effects[22]. Domperidone is not approved by the FDA for use in the United States but is widely used in Europe. To our knowledge, none of the published studies in this area used domperidone as a prokinetic to improve cecal intubation rates. A recent randomized controlled trial which used intramuscular metoclopramide 15 min before capsule ingestion, reported a decrease in GTT with no change in SBTT or complete examination rate[23], reinforcing that it may also be influenced by other variables. In our study, domperidone significantly contributed to reduce the rate of IE. The drug was only administered in patients with delayed gastric passage of the capsule, documented with the RTV. Moreover, there was no significant difference in SBTT among patients who received or did not receive domperidone. The fact that the SBTT was similar in patients receiving or not domperidone (260 min *vs* 297 min, respectively, P = NS) is relevant, because it supports the hypothesis that delayed gastric emptying may be a more determinant factor leading to incomplete SBCE than delayed transit of the capsule in the small bowel; the fact that the transit time of the capsule in the small bowel is not significantly reduced by the prokinetic is also important, because a faster passage of the capsule through the small bowel has been associated with lower diagnostic yield

Table 1 Control group *vs* real time viewer group: Baseline characteristics and outcomes *n* (%)

	Control group (*n* = 307)	RTV group (*n* = 82)	*P*-values
Age (mean ± SD), yr	49.7 ± 20.7	48 ± 20.5	0.518[1]
Gender (male/female)	(136/171)	(32/50)	0.452[2]
History of abdominal surgery	24 (8)	12 (15)	0.083[2]
Inpatient status	38 (12.3)	10 (12.2)	1.00[2]
Clinical indication			0.079[3]
OGIB-occult	117 (38)	26 (32)	
OGIB-overt	46 (15)	6 (7)	
Suspected CD	83 (27)	29 (35)	
CD staging	33 (11)	11 (14)	
Other indications	28 (9)	10 (12)	
Incomplete examination	48 (15,6)	3 (3,7)	0.003[2]
Positive findings	120 (39)	40 (49)	0.081[3]

P-values were calculated using unpaired *t*-test[1], Fisher's exact test[2] (b) and Pearson $\chi^{2,3}$. OGIB: Obscure gastrointestinal bleeding; CD: Crohn's disease; RTV: Real time viewer.

of SBCE[24]. Indeed, Westerhof *et al*[24] found a positive correlation between the diagnostic yield of SBCE and longer small bowel transit time, irrespective of whether the capsule reached the cecum within recording time. In our series, despite the reduction of IE, we did not find a significantly higher diagnostic yield in the RTV group (49% *vs* 39% in the control group). Recently, Gao *et al*[20] showed that delivering the capsule to the duodenum by upper endoscopy using a basket in patients with delayed gastric transit, identified with RTV, improved the rate of complete small-bowel examinations, resulting in higher diagnostic yield of SBCE. We could speculate whether it would be useful to routinely place the capsule in the duodenum with the AdvanCE® from the beginning of the examination. However, this strategy would be both invasive and add costs to a procedure that is already expensive. Moreover, it is not possible to accurately predict to which patients it would be helpful, making it unsuitable to implement as a routine procedure in clinical practice. In our study, only one patient in the RTV group required endoscopic-assisted placement of the capsule into the duodenum. Our results support that to overcome delayed gastric transit time identified by the RTV, non-invasive procedures such as selective administration of oral domperidone to patients with delayed gastric passage of the capsule documented with the RTV, should be the method of choice. This strategy has the merit of strictly selecting the patients to undergo pharmacological and/or flexible endoscopic intervention. Further studies are needed to support the association between complete examination and higher diagnostic yield of SBCE[25]. Although this was not a prospective randomized clinical trial, both groups were homogeneous regarding the most common conditions associated with incomplete SBCE. In conclusion, our results support that the use of RTV to monitor the position of the capsule during SBCE and administration of domperidone in the case of delayed gastric passage, significantly enhances the completion rate of SBCE. Whether such strategy could contribute to improve the diagnostic yield of SBCE will require further investigation.

COMMENTS

Background

In up to 20% of patients undergoing small bowel capsule endoscopy (SBCE) the examination is incomplete. This is a major limitation of this expensive technique, leading to further examinations and expended time and resources. There is ongoing debate on which factors are associated with incomplete examinations and what are the optimal strategies to overcome this issue.

Research frontiers

It has been consistently shown that delayed gastric passage of the capsule is a major factor leading to incomplete examinations. The authors evaluated the effect of the prokinetic drug domperidone for improvement of completion of SBCE, with the routine use of real time viewer (RTV) included in the Data Recorder DR3.

Innovations and breakthroughs

After confirmation with RTV for the presence or absence of the capsule in the stomach at 1 h, selective administration of 10 mg domperidone to those patients with delayed gastric passage of the capsule has the effect to decrease gastric transit time and leads enough to bring down the rate of incomplete examinations, without affecting small bowel transit time.

Applications

This simple and very practical method significantly reduced the rate of incomplete examinations of SBCE. Thus, the authors suggest that the use of the RTV and administration of domperidone for those patients with delayed gastric passage of the capsule should become the standard of practice.

Terminology

SBCE incomplete examination occurs when the capsule does not reach the cecum within the battery lifetime. The RTV is included in the Data Recorder DR3 (Given®), allowing for the real time location of the position of the capsule inside the GI tract. Domperidone is a type II dopamine antagonist which may be used to promote gastric emptying.

Peer review

In this study, Cotter *et al* demonstrate that the systematic use of RTV to recognize patients with delayed gastric passage of the capsule, and selective oral administration of domperidone to these patients is not only an easy and very practical method but also is beneficial for significant reduction of the rate of IE, without affecting small bowel transit time.

REFERENCES

1 **Ladas SD**, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-227 [PMID: 20195992 DOI: 10.1055/s-0029-1243968]

2 **Triester SL**, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. *Am J Gastroenterol* 2005; **100**: 2407-2418 [PMID: 16279893 DOI: 10.1111/j.1572-0241.2005.00274.x]

3 **Rosa B**, Moreira MJ, Rebelo A, Cotter J. Lewis Score: a useful clinical tool for patients with suspected Crohn's Disease submitted to capsule endoscopy. *J Crohns Colitis* 2012; **6**: 692-697 [PMID: 22398099 DOI: 10.1016/j.crohns.2011.12.002]

4 **Triester SL**, Leighton JA, Leontiadis GI, Gurudu SR, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol* 2006; **101**: 954-964 [PMID: 16696781 DOI: 10.1111/j.1572-0241.2006.00506.x]

5 **Long MD**, Barnes E, Isaacs K, Morgan D, Herfarth HH.

Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. *Inflamm Bowel Dis* 2011; **17**: 1855-1862 [PMID: 21830264 DOI: 10.1002/ibd.21571]
6 **Rondonotti E**, Spada C, Cave D, Pennazio M, Riccioni ME, De Vitis I, Schneider D, Sprujevnik T, Villa F, Langelier J, Arrigoni A, Costamagna G, de Franchis R. Video capsule enteroscopy in the diagnosis of celiac disease: a multicenter study. *Am J Gastroenterol* 2007; **102**: 1624-1631 [PMID: 17459022 DOI: 10.1111/j.1572-0241.2007.01238.x]
7 **Burke CA**, Santisi J, Church J, Levinthal G. The utility of capsule endoscopy small bowel surveillance in patients with polyposis. *Am J Gastroenterol* 2005; **100**: 1498-1502 [PMID: 15984971 DOI: 10.1111/j.1572-0241.2005.41506.x]
8 **Marmo R**, Rotondano G, Piscopo R, Bianco MA, Cipolletta L. Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases. *Aliment Pharmacol Ther* 2005; **22**: 595-604 [PMID: 16181299 DOI: 10.1111/j.1365-2036.2005.02625.x]
9 **Saperas E**, Dot J, Videla S, Alvarez-Castells A, Perez-Lafuente M, Armengol JR, Malagelada JR. Capsule endoscopy versus computed tomographic or standard angiography for the diagnosis of obscure gastrointestinal bleeding. *Am J Gastroenterol* 2007; **102**: 731-737 [PMID: 17397406 DOI: 10.1111/j.1572-0241.2007.01058.x]
10 **Eliakim R**, Fischer D, Suissa A, Yassin K, Katz D, Guttman N, Migdal M. Wireless capsule video endoscopy is a superior diagnostic tool in comparison to barium follow-through and computerized tomography in patients with suspected Crohn's disease. *Eur J Gastroenterol Hepatol* 2003; **15**: 363-367 [PMID: 12655255 DOI: 10.1097/01.meg.0000050000.68425.7e]
11 **Pennazio M**, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology* 2004; **126**: 643-653 [PMID: 14988816]
12 **Carey EJ**, Leighton JA, Heigh RI, Shiff AD, Sharma VK, Post JK, Fleischer DE. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. *Am J Gastroenterol* 2007; **102**: 89-95 [PMID: 17100969 DOI: 10.1111/j.1572-0241.2006.00941.x]
13 **Rondonotti E**, Herrerias JM, Pennazio M, Caunedo A, Mascarenhas-Saraiva M, de Franchis R. Complications, limitations, and failures of capsule endoscopy: a review of 733 cases. *Gastrointest Endosc* 2005; **62**: 712-716; quiz 752, 754 [PMID: 16246685 DOI: 10.1016/j.gie.2005.05.002]
14 **Westerhof J**, Weersma RK, Koornstra JJ. Risk factors for incomplete small-bowel capsule endoscopy. *Gastrointest Endosc* 2009; **69**: 74-80 [PMID: 18691709 DOI: 10.1016/j.gie.2008.04.034]
15 **Selby W**. Complete small-bowel transit in patients undergoing capsule endoscopy: determining factors and improvement with metoclopramide. *Gastrointest Endosc* 2005; **61**: 80-85 [PMID: 15672061]
16 **Ben-Soussan E**, Savoye G, Antonietti M, Ramirez S, Lerebours E, Ducrotté P. Factors that affect gastric passage of video capsule. *Gastrointest Endosc* 2005; **62**: 785-790 [PMID: 16246700 DOI: 10.1016/j.gie.2005.07.040]
17 **Mergener K**, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007; **39**: 895-909 [PMID: 17968807 DOI: 10.1055/s-2007-966930]
18 **Postgate A**, Tekkis P, Patterson N, Fitzpatrick A, Bassett P, Fraser C. Are bowel purgatives and prokinetics useful for small-bowel capsule endoscopy? A prospective randomized controlled study. *Gastrointest Endosc* 2009; **69**: 1120-1128 [PMID: 19152909]
19 **Almeida N**, Figueiredo P, Freire P, Lopes S, Lérias C, Gouveia H, Leitão MC. The effect of metoclopramide in capsule enteroscopy. *Dig Dis Sci* 2010; **55**: 153-157 [PMID: 19184428 DOI: 10.1007/s10620-008-0687-y]
20 **Gao YJ**, Ge ZZ, Chen HY, Li XB, Dai J, Ye CA, Xiao SD. Endoscopic capsule placement improves the completion rate of small-bowel capsule endoscopy and increases diagnostic yield. *Gastrointest Endosc* 2010; **72**: 103-108 [PMID: 20304397 DOI: 10.1016/j.gie.2009.12.003]
21 **Rosa BJ**, Barbosa M, Magalhães J, Rebelo A, Moreira MJ, Cotter J. Oral purgative and simethicone before small bowel capsule endoscopy. *World J Gastrointest Endosc* 2013; **5**: 67-73 [PMID: 23424190 DOI: 10.4253/wjge.v5.i2.67]
22 **Camilleri M**, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013; **108**: 18-37; quiz 38 [PMID: 23147521 DOI: 10.1038/ajg.2012.373]
23 **Zhang JS**, Ye LP, Zhang JL, Wang CY, Chen JY. Intramuscular injection of metoclopramide decreases the gastric transit time and does not increase the complete examination rate of capsule endoscopy: a prospective randomized controlled trial. *Hepatogastroenterology* 2011; **58**: 1618-1621 [PMID: 21940331 DOI: 10.5754/hge11081]
24 **Westerhof J**, Koornstra JJ, Hoedemaker RA, Sluiter WJ, Kleibeuker JH, Weersma RK. Diagnostic yield of small bowel capsule endoscopy depends on the small bowel transit time. *World J Gastroenterol* 2012; **18**: 1502-1507 [PMID: 22509082 DOI: 10.3748/wjg.v18.i13.1502]
25 **Handa O**, Naito Y, Okayama T, Yoshida N, Kamada K, Katada Z, Uchiyama K, Ishikawa T, Takagi T, Konishi H, Yagi N, Kokura S, Yoshikawa T. Endoscopic diagnosis of small intestinal diseases. *Clin J Gastroenterol* 2013; **6**: 94-98 [DOI: 10.1007/s12328-013-0364-3]

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BRIEF ARTICLE

Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection

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Abstract

AIM: To clarify the safety and efficacy of repeat endoscopic submucosal dissection (re-ESD) for locally recurrent gastric cancers after ESD.

METHODS: A retrospective evaluation was performed of the therapeutic efficacy, complications and follow-up results from ESD treatment for early gastric cancers in 521 consecutive patients with 616 lesions at St. Luke`s International Hospital between April 2004 and November 2012. In addition, tumor size, the size of resected specimens and the operation time were compared between re-ESD and initial ESD procedures. A flex knife was used as the primary surgical device and a hook knife was used in cases with severe fibrosis in the submucosal layer. Continuous variables were analyzed using the non-parametric Mann-Whitney *U* test and are expressed as medians (range). Categorical variables were analyzed using a Fisher's exact test and are reported as proportions. Statistical significance was defined as a *P*-value less than 0.05.

RESULTS: The number of cases in the re-ESD group and the initial ESD group were 5 and 611, respectively. The median time interval from the initial ESD to re-ESD was 14 (range, 4-44 mo). *En bloc* resection with free lateral and vertical margins was successfully performed in all re-ESD cases without any complications. No local or distant recurrence was observed during the median follow-up period of 48 (range, 11-56 mo). Tumor size was not significantly different between the re-ESD group and the initial ESD group (median 22 mm *vs* 11 mm, $P = 0.09$), although the size of resected specimens was significantly larger in the re-ESD group (median 47 mm *vs* 34 mm, $P < 0.05$). There was a non-significant increase observed in re-ESD operation time compared to initial ESD (median 202 min *vs* 67 min, respectively, $P = 0.06$).

CONCLUSION: Despite the low patient number and short follow-up, the results suggest that re-ESD is a safe and effective endoscopic treatment for recurrent gastric cancer after ESD.

Key words: Endoscopic submucosal dissection; Recurrent gastric cancer; Gastric cancer; Endoscopic mucosal resection; Therapeutic endoscopy

Core tip: Although endoscopic submucosal dissection (ESD) is widely accepted as one of the standard treatments for early gastric cancers, there are few reports on re-ESD in the literature. This study clarifies that re-ESD is a safe and effective endoscopic treatment for locally recurrent gastric cancers after ESD.

Shimamura Y, Ishii N, Nakano K, Ikeya T, Nakamura K, Takagi K, Fukuda K, Suzuki K, Fujita Y. Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; 5(12): 600-604 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i12/600.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i12.600

INTRODUCTION

Early gastrointestinal neoplasms have a low frequency of lymph node and distant metastases, which enables less invasive treatments using therapeutic endoscopy[1-4]. Endoscopic mucosal resection (EMR) is an accepted minimally invasive treatment for early gastrointestinal neoplasms[5-9]. Endoscopic submucosal dissection (ESD) is a safe and effective endoscopic treatment technique that directly dissects the submucosal layer allowing *en bloc* resection of early gastric cancers (EGCs). It improves the quality of life compared with surgical treatment and has an important role in the treatment of EGCs[10-13]. Although ESD yields histologically complete resections, cases of locally recurrent gastric tumors after initial ESD still occur[14-16].

There is currently no established standard treatment for these recurrent lesions, and there are few reports on repeated ESD (re-ESD) procedures. Therefore, the aim of the present study was to clarify the safety and efficacy of re-ESD for locally recurrent gastric cancers.

MATERIALS AND METHODS

Study populations

The clinical database of all patients who underwent ESD for EGCs at St. Luke's International Hospital, Tokyo was retrospectively reviewed. Gastric ESD was performed in a total of 521 consecutive patients with 616 lesions and re-ESD was performed in five locally recurrent gastric cancers between April 2004 and November 2012. Gastric cancer treatment guidelines were applied to all re-ESD cases including those issued in 2004 and 2010 by the Japanese Gastric Cancer Association as well as the proposed extended criteria of Gotoda *et al*[17,18].

Re-ESD methods

Re-ESD was performed with a conventional single-accessory-channel endoscope (GIF-Q260J; Olympus Medical Systems, Tokyo, Japan). Marking dots for the incision were made 3-5 mm outside of lesion margins with a flex knife[19-21] (Flex Knife™, KD-630L; Olympus Medical Systems, Tokyo, Japan) (Figure 1A and B). A solution of 0.4%-0.5% sodium hyaluronate was injected into the submucosal layer beneath the lesion, and circumferential incisions were made around the marking dots with a flex knife. In cases where severe fibrosis prevented injection of the sodium hyaluronate solution, a hook knife (Hook Knife, KD-620LR; Olympus Medical Systems) was used for the dissection of the fibrotic layer[22-24] (Figure 1C). Hemostatic forceps (SDB2422; Pentax Co, Tokyo, Japan) were used during the procedure to control bleeding while the re-ESD was completed (Figures 2 and 3).

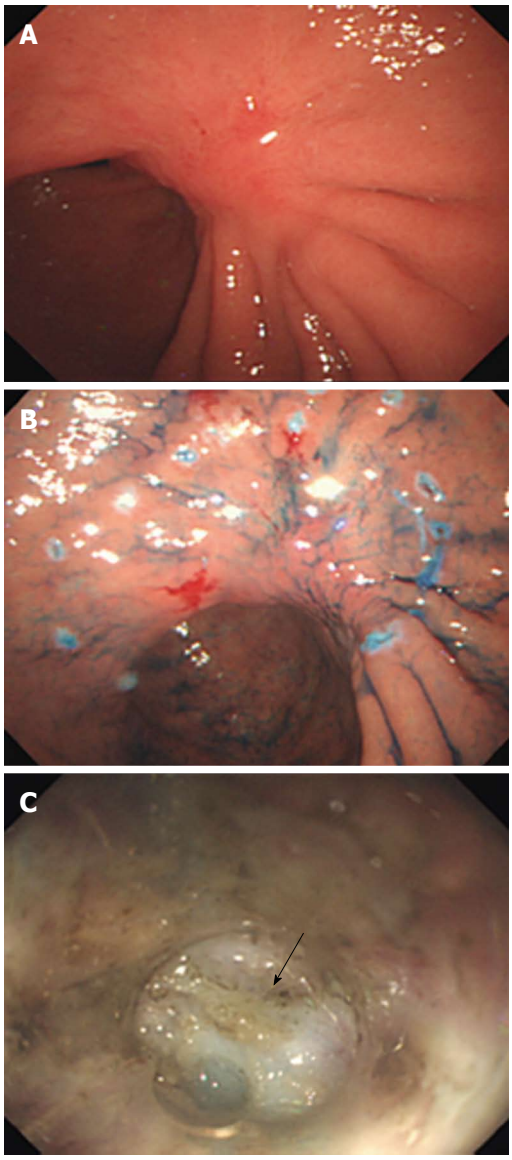

Figure 1 Conventional endoscopic view. A: Showing locally recurrent gastric cancer located in the lesser curvature of the gastric angulus; B: Marking dots for the incision delineating the outside margin of the lesion; C: Severe submucosal fibrosis was observed through a small-caliber transparent hood (arrow).

Pathological assessment

Perpendicular sections at 2 mm intervals of re-ESD specimens were evaluated. Treatment was considered curative if specimens did not indicate invasion deeper than the submucosal or lymphovascular layer or show lateral and vertical margin involvement. *En bloc* resection was defined as resection of the entire lesion in one piece. All resections were categorized according to the National Comprehensive Cancer Network (NCCN) as follows: negative resection margin (R0), microscopic tumor infiltration (R1), and macroscopic residual tumor (R2). Endoscopic examinations and computed tomography (CT) were performed at 6 mo after re-ESD to check for local

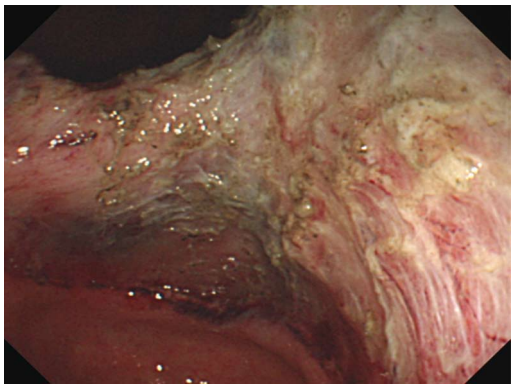

Figure 2 View of the post-endoscopic submucosal dissection ulcer.

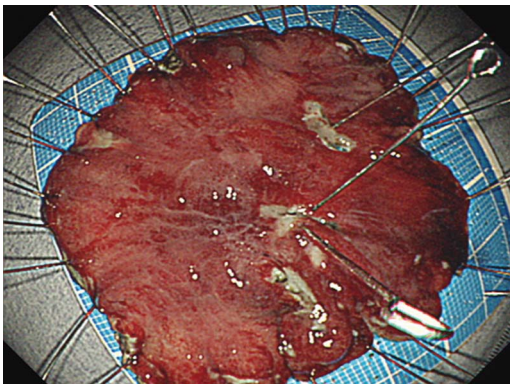

Figure 3 *En bloc* resection of the tumor without any complications.

Table 1 Characteristics of 5 initial endoscopic submucosal dissection cases

Patient No.	Sex	Age, yr	Tumor location	Macroscopic type	Tumor size, mm	Specimen size, mm	Operation time, min	Histological type	Resection margin category
1	Male	78	LB LC	Ⅰ + Ⅱa	23	40	69	Tub2	R0
2	Male	67	LB PW	Ⅱc	8	37	70	Tub1	R0
3	Male	64	Ant PW	Ⅱa + Ⅱc	14	36	47	Tub1	R0
4	Male	76	Ang PW	Ⅱc	65	70	442	Tub2	R1
5	Male	51	Ang LC	Ⅱc	40	45	44	Tub2	R0
Median		67			23	40	69		

Ang: Angulus; Ant: Antrum; LB: Lower body; LC: Lesser curvature; PW: Posterior wall; R0: Negative resection margin; R1: Microscopic tumor infiltration; Tub1: Well differentiated adenocarcinoma; Tub2: Moderately differentiated adenocarcinoma; I: Elevated lesion; IIa: Slightly elevated lesion; IIc: Slightly depressed lesion.

Table 2 Characteristics of re-endoscopic submucosal dissection in 5 cases

Patient No.	Time after initial ESD, mo	Macroscopic type	Tumor size, mm	Specimen size, mm	Operation time, min	Histological type	Resection margin category	Complication
1	44	IIa	22	47	210	Tub2	R0	None
2	9	IIc	8	45	82	Tub1	R0	None
3	14	IIc	11	32	43	Tub1	R0	None
4	12	IIc	27	59	353	Tub1	R0	None
5	4	IIc	42	77	202	Por	R0	None
Median	14		22	47	202			

R0: Negative resection margin; Tub1: Well differentiated adenocarcinoma; Tub2: Moderately differentiated adenocarcinoma; Por: Poorly differentiated adenocarcinoma; IIa: Slightly elevated lesion; IIc: Slightly depressed lesion; ESD: Endoscopic submucosal dissection.

recurrence as well as lymph node and distant metastases.

Statistical analysis

Continuous variables were analyzed using the non-parametric Mann-Whitney *U* test and are expressed as median (range). Categorical variables were analyzed using a Fisher's exact test and are reported as proportion. Statistical significance was defined as a *P*-value less than 0.05.

RESULTS

The characteristics of the initial ESD for 5 cases are summarized in Table 1. One patient was considered R1 with positive horizontal margins, but others were considered R0 with complete resection. Of the initial ESD procedures evaluated, 97.6% (601/616) were *en bloc* resections, 1.3% (8/616) required additional surgical intervention due to an incomplete resection (such as deep invasion of the tumor or lymph vascular invasion), 1.3% (8/616) resulted in postoperative bleeding, and 1.8% (11/616) had perforation. Pathological evaluation resulted in categorization of 95.3% (587/616) of resections as R0, with the remaining 4.7% (29/616) as R1 resections.

Five of the 616 cases developed locally recurrent tumors and were treated by re-ESD (Table 2). The median time interval from the initial ESD to re-ESD was 14 (range, 4-44 mo). *En bloc* resections with free lateral and vertical margins were successfully performed without any complications in all re-ESD cases. Furthermore, there were no local or distant recurrences observed during the follow-up period, at a median of 48 (range, 11-56 mo).

Table 3 Comparisons between re-endoscopic submucosal dissection and initial endoscopic submucosal dissection cases

	Re-ESD (n = 5)	Initial ESD (n = 606)	P value
Tumor size	22 mm	11 mm	0.09
Median (range)	(8-42 mm)	(1.5-65 mm)	
Specimen size	47 mm	34 mm	0.02
Median (range)	(32-77 mm)	(13-92 mm)	
Operation time	202 min	67 min	0.06
Median (range)	(43-353 min)	(10-510 min)	

ESD: Endoscopic submucosal dissection.

There was no significant difference in tumor size between re-ESD cases and all initial cases (22 mm *vs* 11 mm). However, there was a tendency for increased operation time for ESD procedures (202 min *vs* 67 min, $P = 0.06$), and re-ESD specimens were significantly larger than the initial resected specimens (47 mm *vs* 34 mm, $P = 0.02$) (Table 3).

DISCUSSION

ESD is accepted as one of the standard treatments for EGCs, enabling large *en bloc* resections. While this procedure typically results in histologically complete resections, cases of locally recurrent gastric tumors have occurred, with reported incidence rates between 0% and 3%[14-16,25]. Laparoscopic wedge resection, intragastric surgery, and laparoscopic-associated distal gastrectomy are some of the invasive treatment options for locally recurrent gastric cancers[26-28]. A recent report by Higashimaya *et al*[25] documented re-ESD as a minimally invasive, safe and effective procedure in a series of recurrent EGCs. In this study, re-ESD was successfully performed by *en bloc* resection with free lateral and vertical margins without any complications. Treatment of locally recurrent gastric cancers using the re-ESD technique results in less pain, less mortality, and shorter hospital stays, which obviates invasive surgical interventions.

Re-ESD operations tended to take longer than the initial ESD procedures, possibly because the tumor specimens were larger in size. The re-ESD procedure is considered technically difficult as a result of severe fibrosis in the submucosal layer that occurs at the site of the initial ESD. There is currently no efficient ESD method for lesions with submucosal fibrosis, therefore the surrounding tissue should first be dissected to evaluate the anatomical structure, followed by dissection towards the fibrotic lesion. Of additional importance in performing ESD and re-ESD procedures is the selection of an appropriate electrosurgical knife, such as a flash knife, flex knife, dual knife, or as in this study, the hook knife, which was used to dissect the submucosal layer with severe fibrosis.

Several limitations of this study should be noted. First, the study was of a retrospective design involving a limited number of cases from a single center, as the recurrence rate after ESD is very low. Second, even though experienced endoscopists performed the re-ESDs, the success rate depends on the technical proficiency of the endoscopists and the condition of the lesion. Although structural differences may result in variations in technical difficulty, this study did not establish whether the location of the lesion or macroscopic type affects the difficulty of the procedure.

In conclusion, this study demonstrates that re-ESD is a safe and effective endoscopic treatment for locally recurrent gastric cancer after ESD. As a result of the limited case number, further studies evaluating larger sample sizes and longer follow-ups are needed to assess the use of this procedure as a standard treatment for recurrent gastric tumors.

COMMENTS

Background

Endoscopic resection has been accepted as a minimally invasive treatment for early gastrointestinal neoplasms. Endoscopic submucosal dissection (ESD) allows for the dissection of the submucosa with resection of lesions *en bloc*. Although complete resection is expected in this procedure, incidences of local recurrence after the initial ESD are not fully eliminated. There is currently no standard treatment for these locally recurrent gastric cancers.

Research frontiers

There are few reports on repeat endoscopic submucosal dissection (re-ESD) for locally recurrent gastric cancers, and the safety and efficacy of this procedure have not been unequivocally addressed. In this study, the authors encountered 5 cases of recurrent gastric cancers, which were successfully treated with re-ESD procedures.

Innovations and breakthroughs

Repeat ESD for locally recurrent gastric tumors is not yet considered a standard treatment. This study demonstrates the safety and efficacy of the re-ESD technique. Furthermore, comparisons were made of tumor size, resected specimen size, and operation time between initial ESD and re-ESD procedures.

Applications

By demonstrating that re-ESD is a safe and effective therapy, this study presents a strategy for the treatment of patients with recurrent gastric tumors.

Terminology

ESD is a minimally invasive endoscopic technique for the treatment of early gastrointestinal neoplasms allowing direct dissection of the submucosal layer of the lesion with *en bloc* resection. Re-ESD is an endoscopic treatment technique for gastric tumors that locally recur after an initial ESD.

Peer review

The authors describe the treatment of recurrent early gastric cancers with re-ESD in a retrospective study. Five cases of recurrent tumors that were encountered following ESD treatment of early gastric cancer are described and analyzed. The employment of re-ESD procedures resulted in successful treatments with no observed complications, which may facilitate the establishment of this method as a standard treatment for recurrent gastric lesions.

REFERENCES

1 **Folli S**, Morgagni P, Roviello F, De Manzoni G, Marrelli D, Saragoni L, Di Leo A, Gaudio M, Nanni O, Carli A, Cordiano C, Dell'Amore D, Vio A. Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC) for the Italian Research Group for Gastric Cancer (IRGGC). *Jpn J Clin Oncol* 2001; **31**: 495-499 [PMID: 11696619 DOI: 10.1093/jjco/hye107]

2 **Hyung WJ**, Cheong JH, Kim J, Chen J, Choi SH, Noh SH. Application of minimally invasive treatment for early gastric cancer. *J Surg Oncol* 2004; **85**: 181-15; discussion 186 [PMID: 14991872 DOI: 10.1002/jso.20018]

3 **Pech O**, May A, Gossner L, Rabenstein T, Manner H, Huijsmans J, Vieth M, Stolte M, Berres M, Ell C. Curative endoscop-

ic therapy in patients with early esophageal squamous-cell carcinoma or high-grade intraepithelial neoplasia. *Endoscopy* 2007; **39**: 30-35 [PMID: 17252457 DOI: 10.1055/s-2006-945040]
4 **Hirasawa T**, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 2009; **12**: 148-152 [PMID: 19890694 DOI: 10.1007/s10120-009-0515-x]
5 **Tada M**, Murakami A, Karita M, Yanai H, Okita K. Endoscopic resection of early gastric cancer. *Endoscopy* 1993; **25**: 445-450 [PMID: 8261986 DOI: 10.1055/s-2007-1010365]
6 **Inoue H**, Tani M, Nagai K, Kawano T, Takeshita K, Endo M, Iwai T. Treatment of esophageal and gastric tumors. *Endoscopy* 1999; **31**: 47-55 [PMID: 10082409 DOI: 10.1055/s-1999-13647]
7 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]
8 **Katada C**, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. *Gastrointest Endosc* 2005; **61**: 219-225 [PMID: 15729229]
9 **Higuchi K**, Tanabe S, Koizumi W, Sasaki T, Nakatani K, Saigenji K, Kobayashi N, Mitomi H. Expansion of the indications for endoscopic mucosal resection in patients with superficial esophageal carcinoma. *Endoscopy* 2007; **39**: 36-40 [PMID: 17252458 DOI: 10.1055/s-2006-945148]
10 **Neuhaus H**, Costamagna G, Devière J, Fockens P, Ponchon T, Rösch T. Endoscopic submucosal dissection (ESD) of early neoplastic gastric lesions using a new double-channel endoscope (the "R-scope"). *Endoscopy* 2006; **38**: 1016-1023 [PMID: 17058167 DOI: 10.1055/s-2006-944830]
11 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627]
12 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
13 **Isomoto H**, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058]
14 **Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512 [PMID: 12297765]
15 **Oda I**, Oyama T, Abe S, Ohnita K, Kosaka T, Hirasawa K, Ishido K, Nakagawa M, Takahashi S. Preliminary results of multicenter questionnaire study on long-term outcomes of curative endoscopic submucosal dissection for early gastric cancer. *Dig Endosc* 2013; Epub ahead of print [PMID: 23826719]
16 **Onozato Y**, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S, Mori M. Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. *Endoscopy* 2006; **38**: 980-986 [PMID: 17058161 DOI: 10.1055/s-2006-944809]
17 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739]
18 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
19 **Yahagi N**, Fujishiro M, Imagawa A, Kakushima N, Iguchi M, Omata M. Endoscopic submucosal dissection for the reliable en bloc resection of colorectal mucosal tumors. *Dig Endosc* 2004; **16**: S89-S92 [DOI: 10.1111/j.1443-1661.2004.00396.x]
20 **Ishii N**, Itoh T, Horiki N, Matsuda M, Setoyama T, Suzuki S, Uemura M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife for large superficial colorectal neoplasias including ileocecal lesions. *Surg Endosc* 2010; **24**: 1941-1947 [PMID: 20112112 DOI: 10.1007/s00464-010-0883-7]
21 **Ishii N**, Horiki N, Itoh T, Uemura M, Maruyama M, Suzuki S, Uchida S, Izuka Y, Fukuda K, Fujita Y. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife is a safe and effective treatment for superficial esophageal neoplasias. *Surg Endosc* 2010; **24**: 335-342 [PMID: 19517169 DOI: 10.1007/s00464-009-0560-x]
22 **Chiu PW**, Chan KF, Lee YT, Sung JJ, Lau JY, Ng EK. Endoscopic submucosal dissection used for treating early neoplasia of the foregut using a combination of knives. *Surg Endosc* 2008; **22**: 777-783 [PMID: 17704882 DOI: 10.1007/s00464-007-9479-2]
23 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002 DOI: 10.1016/S1542-3565(05)00291-0]
24 **Oyama T**. Counter traction makes endoscopic submucosal dissection easier. *Clin Endosc* 2012; **45**: 375-378 [PMID: 23251884 DOI: 10.5946/ce.2012.45.4.375]
25 **Higashimaya M**, Oka S, Tanaka S, Numata N, Sanomura Y, Yoshida S, Arihiro K, Chayama K. Endoscopic submucosal dissection for residual early gastric cancer after endoscopic submucosal dissection. *Gastrointest Endosc* 2013; **77**: 298-302 [PMID: 23206812 DOI: 10.1016/j.gie.2012.09.003]
26 **Asano M**. Endoscopic submucosal dissection and surgical treatment for gastrointestinal cancer. *World J Gastrointest Endosc* 2012; **4**: 438-447 [PMID: 23189214 DOI: 10.4253/wjge.v4.i10.438]
27 **Yano H**, Kimura Y, Iwazawa T, Monden T. Laparoscopic management for local recurrence of early gastric cancer after endoscopic mucosal resection. *Surg Endosc* 2005; **19**: 981-985 [PMID: 15868263 DOI: 10.1007/s00464-004-8172-y]
28 **Tonouchi H**, Mohri Y, Kobayashi M, Tanaka K, Ohi M, Kusunoki M. Laparoscopy-assisted distal gastrectomy with laparoscopic sentinel lymph node biopsy after endoscopic mucosal resection for early gastric cancer. *Surg Endosc* 2007; **21**: 1289-1293 [PMID: 17278041 DOI: 10.1007/s00464-007-9221-0]

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CASE REPORT

A case of neuroendocrine tumor G1 with unique histopathological growth progress

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Abstract

A gastric neuroendocrine tumor (NET) is generated from deep within the tissue mucosal layers. In many cases, NETs are discovered as submucosal tumor (SMT)-like structures by forming a tumor mass. This case has a clear mucosal demarcation line and developed like a polyp. A dilated blood vessel was found on the surface. The mass lacked the yellow color characteristic of NETs, and a SMT-like form was evident. Therefore, a nonspecific epithelial lesion was suspected and we performed endoscopy with magnifying narrow-band imaging (M-NBI). However, this approach did not lead to the diagnosis, as we diagnosed the lesion as a NET by biopsy examination. The lesion was excised by endoscopic submucosal dissection. The histopathological examination proved that the lesion was a polypoid lesion although it was also a NET because the tumor cells extended upward through the normal gland ducts scatteredly. To our knowledge, there is no previous report of NET G1 with such unique histopathological growth progress and macroscopic appearance shown by detailed examination using endoscopy with M-NBI.

Key words: Neuroendocrine tumor G1; Demarcation line; Polypoid growth; Magnifying narrow-band imaging; Submucosal tumor

Core tip: Neuroendocrine tumors which infiltrate into the mucosa may develop a polypoid appearance mimicking a primary epithelial process.

Hirai M, Matsumoto K, Ueyama H, Fukushima H, Murakami T, Sasaki H, Nagahara A, Yao T, Watanabe S. A case of neuroendocrine tumor G1 with unique histopathological growth progress. *World J Gastrointest Endosc* 2013; 5(12): 605-609 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i12/605.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i12.605

INTRODUCTION

Gastric neuroendocrine tumors (NETs) are relatively rare lesions representing approximately 7% of all neuroendocrine tumors and less than 1% of all stomach neoplasms[1]. Most gastric NETs are found incidentally during upper gastrointestinal (GI) endoscopy[2-6]. Gastric NETs usually have the endoscopic appearance of a submucosal tumor because they grow from deep within the mucosal layers and the tumor mass is yellow. The yellow submucosal tumor (SMT) can be detected by white light and the dilated blood vessel on the surface, which is considered to be a secondary change. Gastric NETs comprise 7%

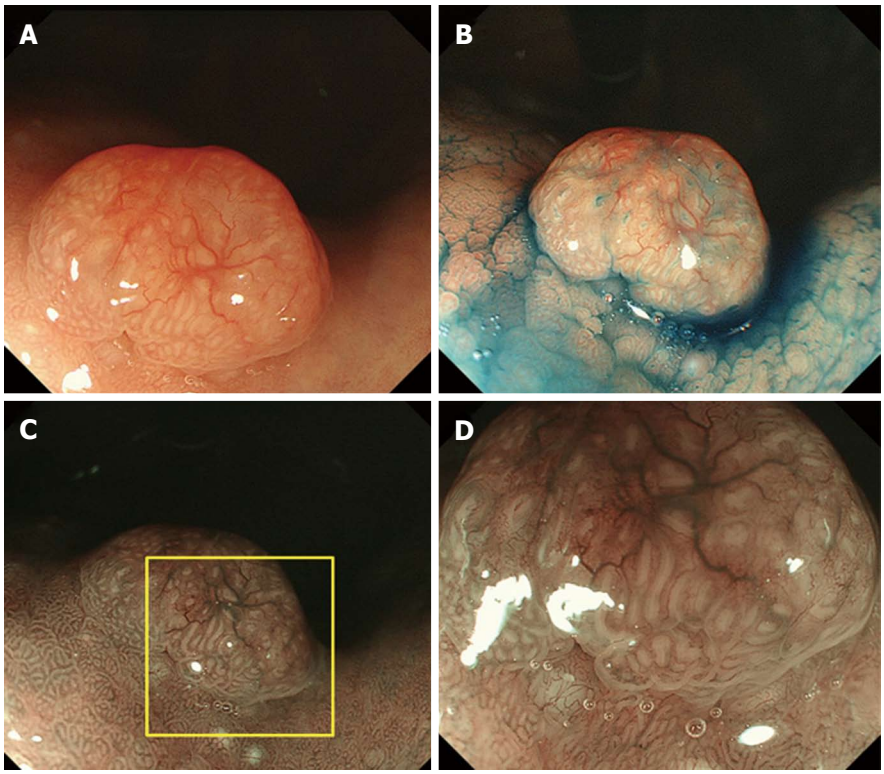

Figure 1 An 8-mm protruded lesion was shown at upper endoscopy. A: Upper endoscopy revealed an 8-mm protruded lesion on the anterior wall of the stomach body. The lesion is the same color as background mucosa and it is not yellow; B: Indigo carmine dye permitted the lesion's demarcation line to become more distinct; C, D: There were dilated vessels on the surface, but neither irregular microvessel patterns nor irregular microsurface patterns were observed by magnifying narrow-band imaging.

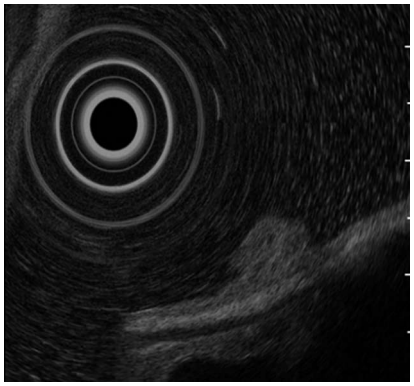

Figure 2 Endoscopic ultrasonography. Endoscopic ultrasonography showed a protruding lesion 8 mm in diameter in the mucosal layer that did not affect the submucosal layer.

of all gastrointestinal NETs and 2% of all excised gastric polyps[7,8]. Randi *et al*[9] classified gastric NETs into three subtypes. Type I NETs typically arise from enterochromaffin-like cell (ECL) hyperplasia, which is stimulated by hypergastrinemia on a background of atrophic gastritis, especially type A gastritis. Type Ⅱ lesions are associated with gastrinomas resulting in Zollinger-Ellison syndrome (ZES). Type Ⅲ lesions are a sporadic disease associated with normal gastrin levels. In type I and Ⅱ diseases, several polyps are often seen in clusters. However, type Ⅲ lesions are usually solitary. The surrounding mucosa may be macroscopically normal, especially in type Ⅲ lesions. Additionally, there may be evidence of atrophy (type I) or associated peptic ulcer (type Ⅱ). Here, we report a case of a type I gastric NET without submucosal tumor shape that extended through the normal gland ducts and developed with polypoid growth.

CASE REPORT

A 61-year-old man presented to his primary care physician with the complaint of mild epigastralgia. An upper GI endoscopy revealed an 8-mm, well-demarcated, protruding lesion on the anterior wall of the stomach body. Therefore, the patient was referred to our hospital. The lesion did not have the reddened appearance of strong inflammation and erosion on the surface like a hyperplastic polyp. The surrounding mucosa was not atrophic. In addition, the lesion was solitary (Figure 1A, B), which contrasts fundic gland polyps that develop as multiple small polyps. Therefore, we performed an endoscopy with magnifying narrow-band imaging (M-NBI) for further evaluation. There were dilated vessels on the surface of the lesion, but there were neither irregular microvessel patterns nor irregular microsurface patterns that indicated neoplastic change under M-NBI (Figure 1C, D). However, the lesion was considered an epithelial neoplasm because the demarcation line was distinct. The pathological evaluation of the biopsy specimen showed the mass was a NET. Endoscopic ultrasonography showed a protruding lesion in the mucosal layer that did not affect the sub-

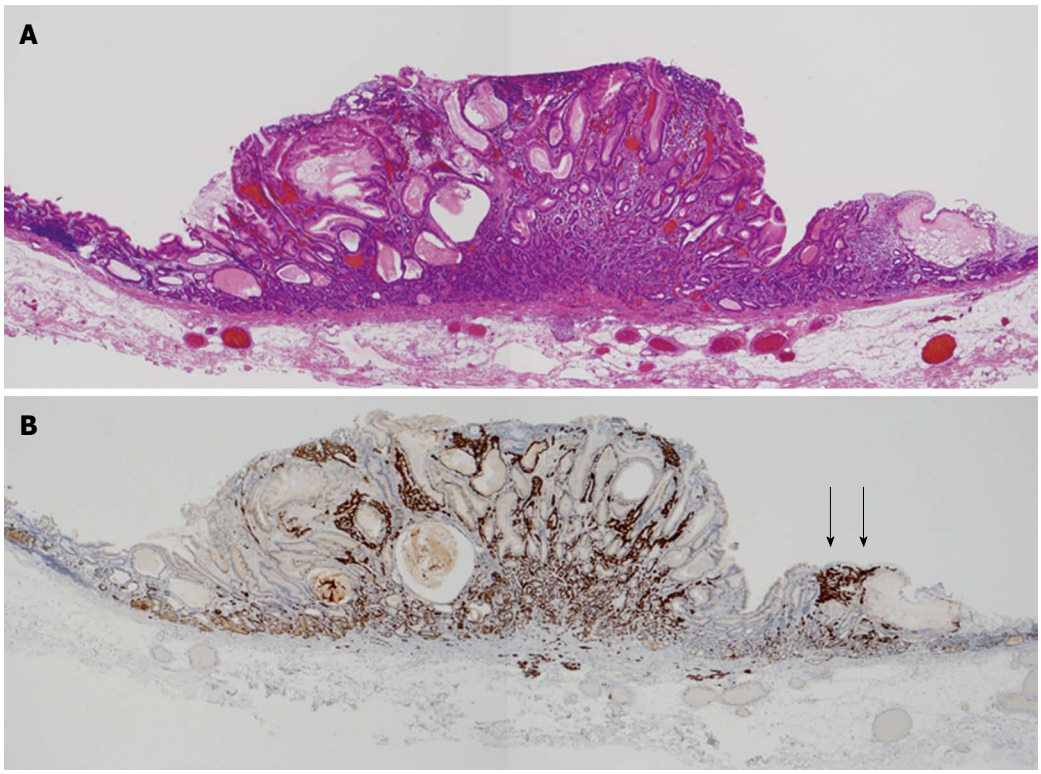

Figure 3 Histological examination of the resected specimen. A: Microscopic examination of the completely resected specimen revealed a neuroendocrine tumor presenting in both the mucosal layer and submucosal layer (hematoxylin and eosin staining); B: Immunohistochemistry for synaptophysin showed that the tumor extended through the normal gland ducts randomly. Enterochromaffin-like cell micro-nests were observed below the normal mucosa (arrow).

mucosal layer (Figure 2).

The laboratory tests revealed normal serum pepsinogen I and serotonin levels, but a markedly increased serum gastrin level (1400 pg/mL; normal range, < 170) and parietal cell antibody level (× 20; normal range, < × 9). The test for anti-Helicobacter pylori IgG was negative. Whole body imaging procedures (CT-scan and abdominal ultrasonography) did not reveal metastatic involvement of any other organ.

We determined the lesion was an atypical gastric NET and conducted endoscopic submucosal dissection. The histopathologic findings of the resected lesion led to the diagnosis of a neuroendocrine tumor of 8 mm × 9 mm. The tumor cells extended through the normal gland ducts scatteredly and infiltrated the submucosal and mucosal layers (Figure 3). Analysis by immunohistochemistry showed positivity for chromogranin A, synaptophysin, and CD56. The Ki-67 proliferation index was 1% (Figure 4). There were numerous ECL hyperplasias and micronests observed under the protruded lesion and in the normal mucosa around the lesion (Figure 3B, yellow arrow). According to the updated Sydney System, intestinal metaplasia was absent. Activity (granulocytic infiltration), inflammation (lymphocytic and mononuclear cell infiltration) and atrophy were moderate at the fornix mucosa and body of the stomach.

As a result of our analysis, we diagnosed the case as a type I neuroendocrine tumor G1 with a very atypical morphological and pathological growth that developed in the background of type A gastritis.

DISCUSSION

Type I NET is the most common lesion type and comprises approximately 70% to 80% of all gastric carcinoids[5,10-12]. According to the World Health Organization's histological classification of gastrointestinal endocrine tumors, a well-differentiated endocrine tumor (synonymous with carcinoid) is defined as an epithelial tumor of usually monomorphous endocrine cells. These tumors have mild or no atypia, grow in the form of solid nests, trabeculae, or pseudoglandular tumors, and are restricted to the mucosa or submucosa[13]. Due to these features, most gastrointestinal NETs have the appearance of submucosal tumors and are visibly yellow by endoscopic examination. However, in the present case, the tumor extended through the normal gland duct scatteredly and did not present a submucosal tumor shape. The result was a well-demarcated polypoid growth presenting like an epithelial neoplasm by endoscopy. The lesion was not yellow and did not present as a tumor except for the mass. Moreover, the lesion did not have the appearance of a hyperplastic polyp and fundic gland polyp.

The percentage of gastric carcinoids amongst all gastric malignancies has increased from 0.3% to 1.77% since the 1950s. The proportion of gastric carcinoids among all gastrointestinal carcinoids has increased from 2.4% to 8.7%[7]. One reason for the increased detection

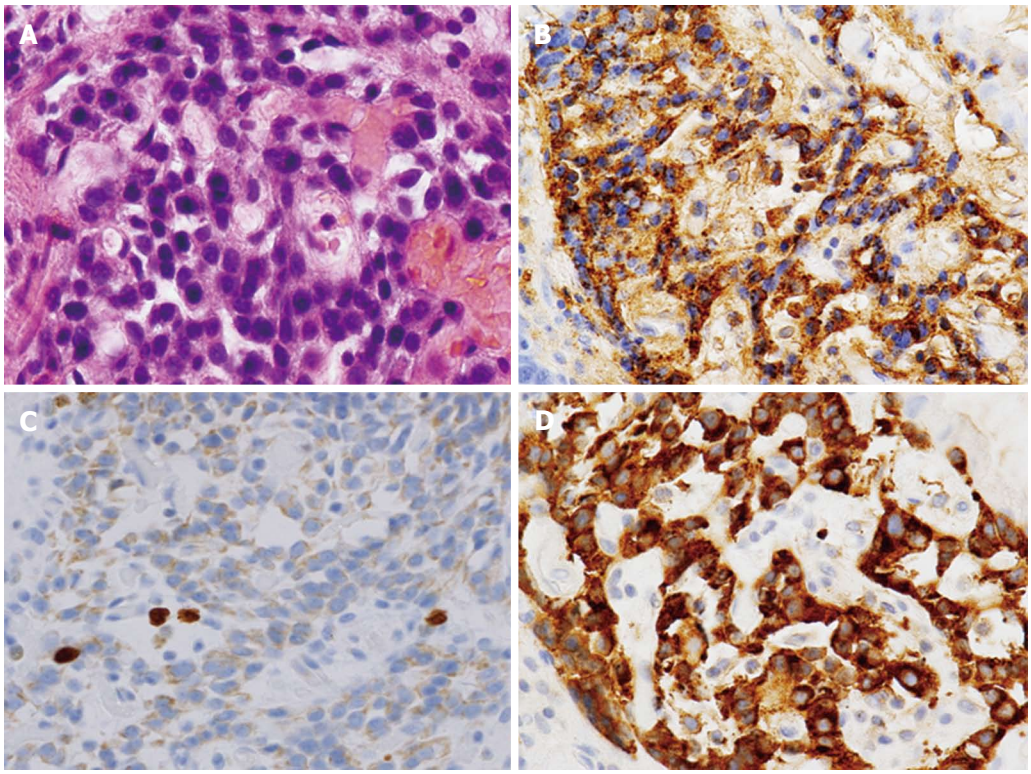

Figure 4 Histological examination of the resected specimen. A: Hematoxylin and eosin staining of the lesion; B: Immunohistochemistry revealed positivity for chromogranin A; C: Only a few positive stained cells were found for Ki-67 and a proliferation index of 1% was evident by immunohistochemistry; D: Immunohistochemistry showed positivity for synaptophysin.

rate is undoubtedly increased awareness of these lesions among pathologists and endoscopists. Additionally, the widespread use of endoscopy and biopsies and the application of immunohistochemical methods have increased detection rates[14]. The increased detection rate has been accompanied by the detection of morphologically and histopathologically untypical lesions. In this report, we present a gastric NET with the unique histopathological growth progress. The lesion did not present as a submucosal tumor but mimicked the endoscopic appearance of epithelial neoplasms.

In the present case, diagnosis by the endoscopic appearance under white light and M-NBI was very difficult. We could not reach a diagnosis until the histopathologic findings of the excised lesion were available. Current methods using M-NBI for the diagnosis of lesions with the endoscopic appearance of typical differentiated adenocarcinoma have been developed and established, especially for the diagnosis of well differentiated adenocarcioma. However, lesions that are confusing and cannot be diagnosed only by endoscopic appearance have been discovered repeatedly. In these cases, biopsies remain necessary. The present case was one such case.

To our knowledge, a NET G1 showing such a macroscopic appearance and histopathological growth progress has not been reported previously. We believe that this is the first report of a NET G1 with such unique histopathological growth progress, including an examination the pathological findings of the excised lesion and the endoscopic appearance under magnifying NBI in detail.

COMMENTS

Case characteristics

A 61-year-old man with the complaint of mild epigastralgia.

Clinical diagnosis

An 8-mm, solitary, well-demarcated, protruding lesion was observed on the anterior wall of the stomach body.

Differential diagnosis

Fundic gland polyp, hyperplastic polyp, adenocarcinoma.

Laboratory diagnosis

A markedly increased serum gastrin level (1400 pg/mL; normal range, < 170) and parietal cell antibody level (× 20; normal range, < × 9); other laboratory tests were within the normal limits.

Imaging diagnosis

Endoscopic ultrasonography showed a protruding lesion in the mucosal layer that did not affect the submucosal layer.

Pathological diagnosis

The biopsy specimen showed the mass was not an epithelial tumor but a neuroendocrine tumors (NETs).

Treatment

The tumor was resected by endoscopic submucosal dissection.

Experiences and lessons

NETs sometimes lack submucosal tumor-like form and mimic epithelial neoplasms if the tumor cells extended through the normal gland ducts scatteredly.

Peer review

NETs which infiltrate into the mucosa may develop a polypoid appearance mimicking a primary epithelial process.

REFERENCES

1 **Nikou GC**, Angelopoulos TP. Current concepts on gastric carcinoid tumors. *Gastroenterol Res Pract* 2012; **2012**: 287825 [PMID: 23316222 DOI: 10.1155/2012/287825]

2 **Modlin IM**, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008; **9**: 61-72 [PMID: 18177818 DOI: 10.1016/S1470-2045(07)70410-2]

3 **Soga J**. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. *Cancer* 2005; **103**: 1587-1595 [PMID: 15742328 DOI: 10.1002/cncr.20939]

4 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959 [PMID: 12569593 DOI: 10.1002/cncr.11105]

5 **Borch K**, Ahrén B, Ahlman H, Falkmer S, Granérus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg* 2005; **242**: 64-73 [PMID: 15973103 DOI: 10.1097/01.sla.0000167862.52309.7d]

6 **La Rosa S**, Inzani F, Vanoli A, Klersy C, Dainese L, Rindi G, Capella C, Bordi C, Solcia E. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol* 2011; **42**: 1373-1384 [PMID: 21531442 DOI: 10.1016/j.humpath.2011.01.018]

7 **Modlin IM**, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol* 2004; **99**: 23-32 [PMID: 14687136 DOI: 10.1046/j.1572-0241.2003.04027.x]

8 **Gencosmanoglu R**, Sen-Oran E, Kurtkaya-Yapicier O, Avsar E, Sav A, Tozun N. Gastric polypoid lesions: analysis of 150 endoscopic polypectomy specimens from 91 patients. *World J Gastroenterol* 2003; **9**: 2236-2239 [PMID: 14562385]

9 **Rindi G**, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993; **104**: 994-1006 [PMID: 7681798]

10 **Zhang L**, Ozao J, Warner R, Divino C. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. *World J Surg* 2011; **35**: 1879-1886 [PMID: 21559999 DOI: 10.1007/s00268-011-1137-0]

11 **Dakin GF**, Warner RR, Pomp A, Salky B, Inabnet WB. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. *J Surg Oncol* 2006; **93**: 368-372 [PMID: 16550587 DOI: 10.1002/jso.20468]

12 **Seya T**, Shinji E, Tanaka N, Shinji S, Koizumi M, Horiba K, Ishikawa N, Yokoi K, Ohaki Y, Tajiri T. A case of multiple gastric carcinoids that could not be preoperatively diagnosed. *J Nippon Med Sch* 2007; **74**: 430-433 [PMID: 18084138 DOI: 10.1272/jnms.74.430]

13 **Solcia E**, Kloppel G, Sobin LH. Histological Typing of Endocrine Tumors. In: World Health Organization. International Histological Classification of Tumors. 2nd ed. Berlin: Springer, 2013 [DOI: 10.1007/978-3-642-59655-1]

14 **Modlin IM**, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. *Gastroenterology* 2005; **128**: 1717-1751 [PMID: 15887161 DOI: 10.1053/j.gastro.2005.03.038]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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