Confocal laser endomicroscopy in pancreatic neuroendocrine tumors
제 23회 대한민국신약개발상 "대상" 수상
한국을 넘어 세계로 뻗어가는 P-CAB, 펩수클루

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앞으로도 다양한 환자의
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치료 여정에 능 활용하겠습니까.
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Typical needle-based confocal laser endomicroscopy images of pancreatic neuroendocrine tumors (PNETs). (A) Typical findings of PNETs. (B) Nesting, trabecular, and glandular arrangements of tumor cell clusters. (C) Surrounding capillary vessels and fibrosis. (D) These findings are consistent with the histological structure (hematoxylin and eosin staining, ×400). (See on page 393−401)
Efficacy and safety of endoscopic submucosal dissection for colorectal dysplasia in patients with inflammatory bowel disease: a systematic review and meta-analysis

Talia F. Malik 1, Vaishnavi Sabesan 2, Babu P. Mohan 3, Asad Ur Rahman 4, Mohamed O. Othman 5, Peter V. Draganov 6, Gursimran S. Kochhar 7

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ESD is safe and effective for the resection of dysplastic lesions in IBD with excellent pooled rates of en-bloc and R0 resection.

• En-bloc resection rate 92.5% (95% CI 87.9–95.4)
• R0 resection rate 81.5% (95% CI 72.5–88)
• Local recurrence rate 3.9% (95% CI 2–7.5)
• Bleeding rate 7.7% (95% CI 4.5–13)
• Perforation rate 5.3% (95% CI 3.1–8.9)

12 Studies
291 Dysplastic lesions
274 IBD Patients

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Confocal laser endomicroscopy in pancreatic neuroendocrine tumors

Advancing Visualization
Advancing Control
Advancing Workflow
Advancing the Art of Endoscopy
E-learning system to improve the endoscopic diagnosis of early gastric cancer

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We developed three e-learning systems for endoscopists to acquire the necessary skills to improve the diagnosis of early gastric cancer (EGC) and demonstrated their usefulness using randomized controlled trials. The subjects of the three e-learning systems were “detection”, “characterization”, and “preoperative assessment”. The contents of each e-learning system included “technique”, “knowledge”, and “obtaining experience”. All e-learning systems proved useful for endoscopists to learn how to diagnose EGC. Lecture videos describing “the technique” and “the knowledge” can be beneficial. In addition, repeating 100 self-study cases allows learners to gain “experience” and improve their diagnostic skills further. Web-based e-learning systems have more advantages than other teaching methods because the number of participants is unlimited. Histopathological diagnosis is the gold standard for the diagnosis of gastric cancer. Therefore, we developed a comprehensive diagnostic algorithm to standardize the histopathological diagnosis of gastric cancer. Once we have successfully shown that this algorithm is helpful for the accurate histopathological diagnosis of cancer, we will complete a series of e-learning systems designed to assess EGC accurately.

Keywords: Endoscopy; Learning; Stomach neoplasms

INTRODUCTION

Gastric cancer is reported to have the fourth highest mortality rate in the world.¹ The stage of gastric cancer at diagnosis is often advanced, except in Japan and Korea. Therefore, the overall 5-year survival rate is <10%.¹ However, the prognosis improves in patients diagnosed at an early stage.² In addition, endoscopic treatment of early gastric cancer (EGC) ensures a patient’s quality of life.³ Hence, early diagnosis of gastric cancer is imperative. Although esophagogastroduodenoscopy (EGD) is useful for detecting EGC,¹ endoscopists have difficulty learning the “technique”, gaining “knowledge”, and “obtaining experience”. These three topics are essential to enable endoscopists to detect EGC using EGD.¹ To address these difficulties, we developed three types of web-based e-learning systems, tested each through randomized controlled trials (RCTs), and demonstrated their usefulness in ensuring correct and precise endoscopic diagnosis of EGC.⁴-⁷ In this review, we introduce the basic diagnostic systems employed in e-learning, the outcomes of RCTs testing the usefulness of these three e-learning systems, and our future projects.

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THE PRINCIPLES FOR DEVELOPING E-LEARNING SYSTEMS FOR THE ENDOSCOPIC ASSESSMENT OF EGC

The core principles of the e-learning system are that endoscopists should acquire “technique”, “knowledge”, and “experience” for the endoscopic diagnosis of EGC. Therefore, we constructed the contents for all e-learning systems imparting “technique”, “knowledge”, and “experience”.

To teach “technique” and “knowledge”, we employed video lectures. The alternative, “acquiring experience” by e-learning, is challenging. Therefore, we speculated that repeated self-study with 100 consecutive cases (100 cases of repeated self-study) could be useful for accumulating experience similar to that employed in machine learning (Fig. 1).³

BASIC DIAGNOSTIC SYSTEMS AND THEIR PERFORMANCE IN “DETECTION”, “CHARACTERIZATION”, AND “PREOPERATIVE ASSESSMENT” EMPLOYED IN THE E-LEARNING SYSTEMS

Detection using conventional white-light imaging
We constructed a color plus surface classification system (CSCS) to characterize mucosal lesions detected using conventional white-light imaging (C-WLI) alone.⁴,⁹ The criteria according to the CSCS were as follows: (1) presence of a well-demarcated lesion with irregularity in color, and (2) presence of a well-demarcated lesion with an irregular surface. If the target met either criterion, the diagnosis was “cancerous”. When both were absent, the diagnosis was “noncancerous” (Fig. 2).⁸

We reported that when we applied these criteria to clinical practice, the sensitivity was 81.0% and the specificity was 88.1%.¹⁰ This diagnostic system can help endoscopists improve their skills in the early detection of EGC.

Characterization using magnifying endoscopy with narrow-band imaging
We established a vessel plus surface classification system (VSCS) (Fig. 3),¹¹ which has already proven helpful in the accurate assessment of EGC¹²,¹³ and in delineating EGC for curative endoscopic resection.¹⁴ The VSCS has been approved through a multi-society consensus as a standardized magnifying endoscopy diagnostic system.¹⁵ The criteria were as follows: (1) presence of an irregular microvascular (MV) pattern with a demarcation line, and (2) presence of an irregular microsurface (MS) pattern with a demarcation line. If the target lesion met either or both criteria, the diagnosis of the lesion was “cancerous”. If both criteria were absent, the diagnosis was “noncancerous”.

We report the diagnostic performance of magnifying endoscopy with narrow-band imaging (M-NBI) with a high-confidence prediction according to the VSCS. The sensitivity was 85.7% and the specificity was 99.4%.¹² The case determined to be a false-negative was a signet-ring cell carcinoma that was pale in color and did not represent either an irregular MV pattern or an irregular MS pattern without a demarcation line. When we excluded the false-negative case that showed a pale superficial mucosal lesion, the sensitivity increased from 85.7%

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Fig. 1. An example of the self-study cases for the diagnosis of 100 cases. (A) One case comprises a set of three slides. The first slide shows one endoscopic photo where one lesion is present. First, the participant should click to choose whether the lesion is cancerous or noncancerous. (B) Immediately after clicking on their choice, an illustration indicating whether the answer is correct or incorrect appears on the second slide. (C) The third slide indicates brief instructions on characterizing the endoscopic findings to diagnose correctly and shows the original endoscopic image again. Adapted from Yao et al. EBioMedicine 2016;9:140–147, according to the Creative Commons license.
Fig. 2. Example of endoscopic images showing the differences between noncancerous and cancerous lesions according to the color plus surface classification system (CSCS) by conventional white-light imaging. (A) Endoscopic findings of a focal atrophic pale mucosal lesion. According to the CSCS, the lesion is not well demarcated without irregularity in color or surface. Therefore, this lesion is diagnosed as noncancerous. (B) Endoscopic findings of a pale early mucosal lesion. There is a well-demarcated lesion; the distribution of the color is irregular and the surface pattern is irregular. Accordingly, this lesion is diagnosed as cancerous. Adapted from Yao et al. Gastric Cancer 2017;20(Suppl 1):28–38, according to the Creative Commons license.

Fig. 3. Vessel plus surface classification system (VSCS) by magnifying narrow-band imaging. Microvascular and microsurface patterns are classified as regular/irregular/absent. If the findings fulfill the following criteria, a cancer diagnosis is made (arrow, demarcation line): (1) presence of an irregular microvascular (MV) pattern with a demarcation line and (2) presence of an irregular microsurface (MS) pattern with a demarcation line. Otherwise, the diagnosis is noncancerous. Adapted from Muto et al. Dig Endosc 2016;28:379–393, according to the Creative Commons license.
to 100%. Hence, when the VSCS is used for diagnosis using M-NBI, M-NBI is deemed an optical biopsy.

Preoperative assessment to select the optimal therapeutic strategy for EGC (endoscopic vs. surgical resection) for predicting submucosal cancer

To determine the indications for endoscopic resection, we need to assess the (1) histological findings (differentiated vs. undifferentiated type), (2) size, (3) depth of invasion (mucosal vs. submucosal invasion), and (4) presence or absence of an ulcer.

We focused on the endoscopic diagnosis of the depth of invasion by chromoendoscopy, referring to the “non-extension sign (NES)”\(^1\). The NES is a phenomenon characterized by focal thickness and rigidity of the submucosal layer caused by massive submucosal invasion of cancerous tissue. When endoscopic air is insufflated and the stomach is distended, the form of extension differs depending on the depth of the cancer. For example, T1a-T1b1 cancers and noncancerous mucosa are well extended and flattened. However, two distinct patterns are found in the case of T1b2 cancer. (1) The T1b2 submucosal invasive cancer is not flattened and is poorly extended, forming a trapezoid elevation (Fig. 4). (2) The tips of the mucosal folds, which converge onto the trapezoid elevation, become elevated (Fig. 4). If the endoscopic findings show both or either of these findings, the lesion is determined to be NES-positive. If both findings are negative, it is assessed as NES-negative. The sensitivity of NES for predicting a T1b2 cancer was 92.0% (95% confidence interval [CI], 87.0%–97.0%), and the specificity was 97.7% (95% CI 96.7%–98.8%).\(^2\)

OUTCOMES OF RCT TESTING THE USEFULNESS OF THE E-LEARNING SYSTEMS

The first e-learning system: “detection”

In the first step, mucosal lesions suspicious for EGC should be detected using C-WLI, which is commonly available worldwide. Accordingly, the first e-learning system was designed to enable endoscopists to increase the detection of EGC using C-WLI alone.\(^3\) The principles and details of this e-learning system are comprehensively reported elsewhere.\(^4\)

In this study, participants took a pretest and were randomly assigned to either the e-learning group (ELG) or non-e-learning group (NELG). Only the participants assigned to the ELG could perform e-learning. After 2 months, both groups underwent a posttest. Eligibility was determined by 515 endoscopists from 35 countries, and 332 endoscopists were enrolled in the trial. We then randomly assigned 166 participants to either the ELG or NELG. Finally, we analyzed the data obtained from 151 participants who completed e-learning (ELG) and 144 (NELG) who did not have access to e-learning (Fig. 5). The mean improvement rate±standard deviation in the ELG was 1.24±0.26, which was significantly higher than that of the NELG (1.00±0.16) (\(p<0.001\), unpaired \(t\)-test) (Table 1).\(^5\)

The second e-learning system: characterization

After detecting a suspicious mucosal lesion by C-WLI, the next process should be “characterization”. M-NBI helps differentiate between cancerous and noncancerous lesions\(^6,7\) and reduces the number of biopsies.\(^8\)

Although VSCS is simple, endoscopists require substantial effort to acquire “technique”, “knowledge”, and “experience” to be accustomed to this system. Because no systematic learning

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Fig. 4. A representative endoscopic image of early gastric cancer with deep submucosal invasion (T1b2) showing the non-extension sign. (A) The strongly distended gastric wall is gradually elevated toward the submucosa-invasive area (yellow arrow), which has a trapezoid appearance. (B) This endoscopic finding is well supported by the histological findings of the resected specimen. The depth of invasion is 4,500 μm from the muscularis mucosae in this case (hematoxylin and eosin staining, ×20).
Fig. 5. Flowchart of the enrollment of participants, randomization, and analysis records.

Table 1. Degree of improvement in test scores between the e-learning and non-e-learning groups

<table>
<thead>
<tr>
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<th>E-learning group</th>
<th>Non-e-learning group</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean±SD (%)</td>
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<tr>
<td>Overall</td>
<td>151</td>
<td>1.24±0.26</td>
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<tr>
<td>Lower score group</td>
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<td>1.34±0.29</td>
</tr>
<tr>
<td>Higher score group</td>
<td>65</td>
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</tr>
<tr>
<td>Less experienced group</td>
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<td>1.28±0.26</td>
</tr>
<tr>
<td>More experienced group</td>
<td>67</td>
<td>1.19±0.26</td>
</tr>
<tr>
<td>Asia-Oceania</td>
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<td>1.33±0.34</td>
</tr>
<tr>
<td>Europe</td>
<td>22</td>
<td>1.18±0.24</td>
</tr>
<tr>
<td>Latin America</td>
<td>97</td>
<td>1.23±0.23</td>
</tr>
</tbody>
</table>

Adapted from Yao et al. EBioMedicine 2016;9:140–147, according to the Creative Commons license.<sup>3</sup>

SD, standard deviation.

<sup>a</sup>p<0.001 for the e-learning group versus the non-e-learning group.

<sup>b</sup>p=0.002 for the e-learning group versus the non-e-learning group.

system has proven its usefulness through a well-designed clinical trial, we developed an e-learning system for EGC diagnosis using M-NBI and tested its efficacy using an RCT. Endoscopists from all over Japan participated in this study. After the participants received test 1, they were randomly allocated to either the ELG or NELG. The ELG could learn the M-NBI diagnosis through the e-learning system. After the ELG finished e-learning, both the ELG and NELG took test 2. A total of 395 endoscopists from 77 facilities who completed test 1 were randomly assigned to the ELG (n=198) or NELG (n=197) (Fig. 6). The change in the score in test 2 of the ELG was 7.4 points, which was significantly higher than that (0.14 points) of the NELG (p<0.001, unpaired t-test) (Fig. 7). This trial demonstrated the usefulness of this second e-learning system for improving the diagnosis of EGC by M-NBI.

The third e-learning system: “preoperative diagnosis”

After completing two e-learning systems for “detection” and
“characterization”, we were confident that acquiring “technique”, “knowledge”, and “experience” is beneficial to endoscopists to improve the diagnosis of EGC. Teaching “technique” and “knowledge” by giving lectures using recorded video clips in an e-learning context is not so difficult. However, the “accumulation of experience” is difficult for every endoscopist. The experience of endoscopists in hospitals with few cases is limited. We assumed that for predicting submucosal EGC according to endoscopic findings, “experience” is essential for acquiring the diagnostic ability in addition to learning the “technique” and gaining the “knowledge”.

Accordingly, in contrast to the two previous RCTs, the purpose of the third study was to investigate whether this “accumulation of experience” is independently affected in improving the ability of the endoscopist to predict submucosal EGC. We carried out an RCT that included 423 endoscopists from 93 institutions all over Japan. After the participants took a pretest, they learned the “technique” and “knowledge” by watching recorded videos and the received posttest 1. After posttest 1, we randomly assigned the participants to either the self-study group (SSG) or non-self-study group (NSSG). Only participants

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Fig. 6. Flowchart of the enrollment of participants, randomization, and analysis records.

Fig. 7. The changes in accuracy between tests 1 and 2 in the e-learning and non-e-learning groups. The mean accuracy with 95% confidence intervals in tests 1 and 2 for both groups. The change in accuracy in tests 1 and 2 is significantly higher in the e-learning group than in the non-e-learning group (Δ7.4 vs. Δ0.14 points, respectively; \( p<0.001 \), unpaired t-test). Adapted from Nakanishi et al. Endoscopy 2017;49:957–967, permission from the publisher.
in the SSG could log on to the self-study training system, where they practiced 100 case quizzes. After completing the self-study, participants in the SSG and NSSG received posttest 2. The primary endpoint was the difference in the mean scores of posttest 2 between the SSG and NSSG. The maximum score was 100.

A total of 423 endoscopists who completed the pretest were included in the study. Of these, 415 completed posttest 1 and were randomly allocated to either the SSG \( (n=208) \) or NSSG \( (n=207) \). Finally, 204 participants from the SSG and 205 from the NSSG were analyzed (Fig. 8). After watching the lecture videos, the mean score increased from 72 points on the pretest to 77 points on posttest 1. The posttest 2 score of the SSG participants was 80 points, which was significantly higher than that (76 points) of the NSSG participants \( (p<0.001, \text{unpaired } t\text{-test}) \) (Fig. 9).

The third study showed that the “accumulation of experience”, achieved by repeated practice using the 100-case self-study training, consolidated the learning “technique” and “knowledge” and increased the diagnostic ability of endoscopists of EGC.

DISCUSSION AND FUTURE PLANS

In this article, we introduced three web-based e-learning systems to teach the endoscopic diagnosis of EGC, focusing on “detection”, “characterization”, and “preoperative diagnosis”. We clearly demonstrated that these three e-learning systems are useful as shown by RCTs. Before introducing an e-learning system, we also demonstrated a basic diagnostic system and evidence for each system because an e-learning system should be constructed with concrete diagnostic procedures proven useful.
Fig. 9. Changes in the mean scores with 95% confidence intervals (CIs) for the pretest, posttest 1, and posttest 2. The p values are for comparisons between the two tests. In the self-study and non-self-study groups, the mean scores for posttest 2 (80.3 and 75.8) and posttest 1 (77.4 and 77.1) are significantly higher than those for the pretest (72.1 and 71.4; p<0.001, paired t-test). In the self-study group, the mean score for posttest 2 (80.3) is significantly higher than that for posttest 1 (77.4; p<0.001, paired t-test). In the non-self-study group, the mean score for posttest 2 (75.8) is significantly lower than that for posttest 1 (77.1; p=0.012, paired t-test). Adapted from Kato et al. Endosc Int Open 2019;7:E871–E882, according to the Creative Commons license.7

in well-designed clinical trials.

The e-learning included three components: “technique”, “knowledge”, and “experience”. The endoscopist can learn “technique” and “knowledge” by viewing lecture videos; however, it is difficult for the endoscopist to acquire “experience”. Accordingly, we developed a 100-case self-training program. The efficacies of the first and second e-learning systems were assessed after participants, who were allocated to the ELG, studied “technique”, “knowledge”, and “experience” altogether. The third e-learning system trial was designed differently from the previous trials because we speculated that 100-case self-training could increase the learning effect. Accordingly, we randomized the participants after completing the video lectures to independently assess the efficacy of the 100-case self-training program. Interestingly, the video lectures significantly improved the test scores; however, this learning effect did not last long without experience. The participants who completed the 100-case self-training program showed significantly greater improvement in the test scores. These results indicated that acquiring “technique” and “knowledge” is not enough to achieve improved diagnostic ability and that accumulating “experience” is mandatory.18

Conventional instruction, such as teaching in clinical practice by a senior endoscopist, hands-on training using models or patients, attending lectures, and reading papers or books, is useful for imparting “knowledge” and “technique”. However, the number of learners is limited, and these forms of instruction cannot provide an accumulation of “experience”. As described previously, e-learning offers several advantages over conventional instruction. It can provide “technique” and “knowledge” by watching video clips that are easy for endoscopists to understand, and repeated training programs can be helpful for endoscopists to accumulate “experience”, which is similar to machine learning. Moreover, the number of learners is not limited, and they can access e-learning whenever and wherever they prefer.

One of the limitations of these trials is that outcome measurement was carried out using test scores on the Internet. We have not yet assessed the improvements in clinical practice
after e-learning. We aimed to plan clinical trials to assess the improvement in endoscopic diagnosis in clinical practice after participants completed e-learning.

We will consider investigating the efficacy of an e-learning system to improve the histopathological diagnosis of EGC, as this is the gold standard for endoscopic diagnosis. As previously mentioned, a diagnostic system should first be constructed. To date, no standardized diagnostic systems have been established. We developed a comprehensive algorithm for making a histological diagnosis of gastric cancer (Fig. 10). We tested whether the algorithm can function as a standard diagnostic system for e-learning content. In the near future, we will initiate the RCT by inviting international pathologists (UMIN000044545). If this trial is successfully completed, our series of e-learning systems for improving the endoscopic and histopathological diagnosis of EGC can be finalized.

CONCLUSIONS

We developed an e-learning system to improve the endoscopic diagnosis of EGC and demonstrated its usefulness.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

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REFERENCES

INTRODUCTION

Recent advances in medical technology have made endoscopy a preferred and accessible option for the evaluation and treatment of various gastrointestinal lesions. From image-enhanced endoscopy to advanced therapeutic endoscopy, what was once considered a boundary has been continually challenged and expanded. Despite these advances, the biggest limitation of using flexible endoscopes for endoscopic intervention lies in their innate nature. In freely moving gastrointestinal organs with tortuosity, endoscopist manipulations cannot be accurately delivered to the distal tip of the flexible endoscope. Moreover, having only one working channel permits the use of only one device, even in challenging therapeutic procedures.

Cap-assisted endoscopy refers to a procedure in which a short tube made of a polymer (mostly transparent) is attached to the distal tip of the endoscope to enhance its diagnostic and therapeutic capabilities. It is reported to be particularly useful in: (1) minimizing blind spots during screening colonoscopy, (2) providing a constant distance from a lesion for clear visualization during magnifying endoscopy, (3) accurately assessing the size of various gastrointestinal lesions, (4) preventing mucosal injury during foreign body removal, (5) securing adequate workspace in the submucosal space during endoscopic submucosal dissection or third space endoscopy, (6) providing an optimal approach angle to a target, and (7) suctioning mucosal and submucosal tissue with negative pressure for resection or approximation. Here, we review various applications of attachable caps in diagnostic and therapeutic endoscopy and their future implications.

Keywords: Caps; Endoscopic mucosal resection; Foreign body; Hemostasis; Magnifying endoscopy

The role of cap-assisted endoscopy and its future implications

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Cap-assisted endoscopy refers to a procedure in which a short tube made of a polymer (mostly transparent) is attached to the distal tip of the endoscope to enhance its diagnostic and therapeutic capabilities. It is reported to be particularly useful in: (1) minimizing blind spots during screening colonoscopy, (2) providing a constant distance from a lesion for clear visualization during magnifying endoscopy, (3) accurately assessing the size of various gastrointestinal lesions, (4) preventing mucosal injury during foreign body removal, (5) securing adequate workspace in the submucosal space during endoscopic submucosal dissection or third space endoscopy, (6) providing an optimal approach angle to a target, and (7) suctioning mucosal and submucosal tissue with negative pressure for resection or approximation. Here, we review various applications of attachable caps in diagnostic and therapeutic endoscopy and their future implications.

Keywords: Caps; Endoscopic mucosal resection; Foreign body; Hemostasis; Magnifying endoscopy
MINIMIZATION OF BLIND SPOTS VIA ENHANCED MUCOSAL EXPOSURE

Colonoscopy reduces the incidence and mortality rates of colorectal cancer. However, post-colonoscopy colorectal cancer accounts for 7.2% to 9% of all colorectal cancers. A substantial proportion of premalignant or malignant lesions are overlooked during screening colonoscopy, even by experienced endoscopists. Several reasons for this have been proposed, including the small size or flatness of the lesions, insufficient withdrawal time, or poor bowel preparation.

Mucosal exposure is important in improving adenoma detection rates (ADR) and reducing miss rates. Transparent caps are among the most extensively studied distal attachments for improving mucosal exposure. It can press against the colonic folds, thereby improving the view of the mucosa on the oral side of the folds and allowing for the detection of adenomas previously hidden in blind spots. It can also help manage the “hooking” of the folds, in which the end of the colonoscope will pull back the colonic folds more effectively during the process of straightening the tortuous colonic segment (Fig. 1). This can also result in the exposure of previously uncharted blind spots for further detection of adenomas.

As such, cap-assisted colonoscopy can provide a clear benefit in maximizing ADR, and previous studies have largely agreed. A randomized, two-center trial from 2015 reported an ADR of 42% for cap-assisted colonoscopy, which is higher than the standard ADR of 30% for males and/or 20% for females as proposed by the American Society for Gastrointestinal Endoscopy for quality control. A more recent prospective, multicenter, randomized controlled trial showed that cap-assisted colonoscopy, when combined with chromoendoscopy, markedly improved the ADR by 9.5% in comparison to the standard colonoscopy group.

Earlier analyses reported a marginal benefit of cap-assisted colonoscopy over conventional colonoscopy, both in polyp detection and cecal intubation time, and recent publications have also shown that the ADR of cap-assisted colonoscopy was significantly higher, especially when trials that did not meet quality standards were excluded.

PROVISION OF A CONSTANT DISTANCE FROM A LESION FOR CLEAR VISUALIZATION

Magnifying endoscopy, which can be combined with narrow-band imaging or chromoendoscopy, allows more accurate histologic prediction and/or estimation of invasion depth for colorectal neoplasia. Today, even a conventional high-definition colonoscope (CF-HQ290; Olympus Co.) provides an optical magnification function, the so-called near-focus mode,
which can enlarge images up to 75 times their original size when displayed on a 19-inch monitor without sacrificing image quality.

Acquiring clear images with magnifying endoscopy is occasionally challenging. From the lumens of the intestines to consistent interference from respiratory movements, aortic pulsations, and peristalsis, endoscopists struggle with unfavorable circumstances during examination. Thus, a key factor in magnifying endoscopy is ensuring that magnified images are in focus. To achieve this, the attachment of a black rubber cap at the end of the endoscope can be very helpful (Fig. 2). Attaching a cap at the end of the endoscope allows the endoscopist to fix the distance between the lens and mucosal surface at approximately 2 mm, a point of focus at which good magnification of the endoscopic image can be obtained. Whenever a desired lesion is found, the endoscopist can direct and contact the black rubber cap tip to the mucosal surface while applying zoom mode (Fig. 3). Simultaneously, the “red out phenomenon”, which refers to blurred visualization due to direct tissue attachment or suction all the way to the lens, can be minimized. The caps are also soft and round, which minimizes damage to the friable mucosa. Attaching a cap helps endoscopes stay on focus throughout the exam, allowing endoscopists to quickly and easily obtain images of desired lesions that are on focus.

ACCURATE MEASUREMENT OF COLORECTAL LESIONS

The size of colorectal neoplastic polyps is correlated with colorectal cancer risk; the larger the polyp, the greater the chance of malignancy. It requires shorter follow-up intervals after the removal of adenomas 1 cm in size or greater compared with smaller adenomas. Furthermore, the European Society of Gastrointestinal Endoscopy guidelines recommend different methods of polyp removal depending on the polyp size: cold forceps polypectomy for 1 to 3 mm polyps and cold snare polypectomy for 4 to 9 mm polyps. Thus, an accurate measurement of ad-

Fig. 2. Endoscopic hood with fixed distance of 2 mm (MAJ-1989, 1990, 1991, and 1992; Olympus Co.).

Fig. 3. Endoscopic image of a sessile serrated lesion (A) and its magnified image (B). The black rubber cap helps to keep a steady focal length during magnifying endoscopy.
enoma size can affect the colorectal polyp treatment strategies employed and follow-up after resection.

The most used method of size measurement in daily practice is visual estimation during colonoscopy. However, accurate visual estimation is challenging because of barrel distortion from the fisheye lenses of endoscopes.

Various add-on tools, such as endoscopic rulers, open forceps, and graduated needles, have been used to improve accuracy in lesion size measurement; however, an add-on colonoscopy cap is the most accessible and affordable option thus far. In a prospective randomized trial, Han et al. placed a transparent grid with 1-mm-spaced grid lines inside a colonoscopic cap upon encountering a polyp to measure its size (Fig. 4). Compared with the control group, measurements taken with colonoscopic caps were significantly more accurate than visual estimation. While measuring with grid paper within the cap prolonged measurement time, the authors suggested that it was still significantly shorter than the time it took endoscopists to use other add-on devices, such as forceps, while providing higher accuracy in measurement than visual estimation.

**PROTECTION OF NEARBY MUCOSA DURING FOREIGN BODY REMOVAL**

The attachment of an endoscopic cap is effective in protecting the esophageal or pharyngeal mucosa from lacerations that may occur during the retrieval of sharp objects. The endoscopist would grab the sharpest edge of the object with forceps or a grasper, then retrieve it to the confines within the cap to “harbor” the sharpest edge (Fig. 5). This minimizes the damage that

![Fig. 4](image_url)
foreign bodies can cause to the normal mucosa during the retrieval process (Fig. 6). In a recent randomized controlled trial in 2021, transparent cap-assisted endoscopy was demonstrated to be a safe and effective method in the management of foreign bodies in the upper esophagus, with a significantly shorter retrieval and operation time, higher technical success and en-bloc removal rates, and a lower rate of procedure-related mucosal tear and bleeding.\(^\text{24}\) In another propensity score matching study, transparent cap-assisted endoscopy was non-inferior to conventional endoscopy in its success rates for foreign body removal while displaying shorter procedure times and higher rates of clear endoscopic view.\(^\text{25}\)

**SECURING ADEQUATE WORKSPACE IN THE SUBMUCOSAL LAYER**

In a traditional sense, endoscopy involved two spaces: the gut-intestinal lumen represented the “first” space and the peritoneal cavity the “second”. However, with advancements in technology, a new arena for endoscopic maneuvers is emerging within the wall of the gut. “Third space endoscopy” refers to procedures that take place in the intramural space, a normally enclosed space that must be created by either dissecting or expanding the submucosal layer between the mucosa and muscularis propria (Fig. 7).\(^\text{26,27}\)

In 2007, a new concept of natural orifice transluminal endoscopic surgery was proposed for peritoneoscopy through the stomach.\(^\text{28}\) This technique was later applied as peroral endoscopic myotomy (POEM) for the treatment of achalasia.\(^\text{29,30}\) Following the basic concept of the POEM procedure, the tunneling technique for approaching the third space for en-bloc resection of the tumors arising from the muscularis propria was also reported.\(^\text{31}\) One of the greatest benefits of submucosal tunneling endoscopic resection is that it provides a good workspace within the submucosal layer with a mucosal safety flap valve.

The pocket creation method is a useful method for ESD,
which can achieve a higher complete resection rate, higher en-bloc resection rate, shorter procedure time, faster dissection speed, and lower overall adverse event rate than conventional ESD. This technique can be characterized as entering and dissecting the submucosal layer to make a pocket using a transparent cap after a small mucosal incision, allowing the entrance of the endoscope tip. An attachable cap with a tapered end (Fig. 8) is recommended for this technique; however, a conventional transparent cap with a normal caliber is also available based on operator preference. The method can yield several advantages over conventional ESD, including prevention of submucosal solution leakage, providing good traction of the submucosal tissue, enabling a tangential approach against the muscularis propria by adjusting the direction of the endoscope inside the pocket, and stable control of the endoscope regardless of heart beat or respiration.

PROVIDING AN OPTIMAL APPROACH ANGLE TO A TARGET

The approach angle between the endoscope tip and the target is an important factor in successful endoscopic procedures. However, adjusting the approach angle while managing a flexible endoscope is challenging, even within a freely movable gastrointestinal lumen.

Endoscopic application of hemoclips, called endoclips, is a mechanical hemostatic method used to clamp bleeding vessels; however, their success rate is occasionally dependent on the anatomical location of the lesion. For instance, in lesions on the posterior wall of the gastric body or duodenal papilla, the endoscope is likely to be parallel or extremely tangential to the lesion. Fuke et al. reported that of 168 patients with peptic ulcers, 10 of the 88 patients with posterior wall ulcers failed to achieve hemostasis, compared with four of the 80 patients with ulcers in other areas. In that regard, attachable caps can help the endoscope reach a desired lesion more perpendicularly. In their study, Kim et al. showed that while there were no statistically significant differences between the hemostasis rates of patients treated with the cap and those without, placing a transparent cap at the end of the endoscope helped endoscopists clip a lesion too tangential to be clipped with greater ease due to having a superior view. Having a cap also decreased the risk of accidental mucosal damage during clip deployment, as endoscopists would simply cover the clip within the cap prior to its use.

A perpendicular approach to the desired lesion does not always involve the bleeding site in an area with a parallel or tangential angle. In a study comparing cap-assisted endoscopy with conventional endoscopy when visualizing the ampulla of Vater, cap-assisted endoscopy displayed a higher visualization rate, shorter examination time, and higher detection rate of ampullary adenoma. In fact, cap-assisted endoscopy was non-inferior in its ability to completely visualize the major duodenal papilla in comparison to side-viewing endoscopy while displaying better scores for mucosal pattern examination and overall satisfaction.

One of the challenging steps in the placement of a self-expandable metal stent for malignant obstruction is the passage of the guidewire through a lumen-pending obstruction. In this procedure, shortening and unlooping of the colon are important for aligning the axis of the narrowed lumen and working channel of the endoscope. The “red out phenomenon” can frequently occur during manipulation because the endoscope lens is likely to touch the surface of the tumor; however, the use of an attachable cap can prevent vision loss during cannulation.

SUCTIONING MUCOSAL AND SUBMUCOSAL TISSUE WITH NEGATIVE PRESSURE FOR RESECTION OR APPROXIMATION

Ligation is one of the most effective hemostatic methods. However, mechanical hemostasis via ligation is challenging, particularly in flat or depressed lesions. In such cases, suctioning the
bleeding point, including the adjacent tissue, into an attachable cap with negative pressure can be a good solution for successful ligation. Endoscopic band ligation is one of the most effective methods of bleeding control in variceal bleeding, Dieulafoy’s lesion, Mallory-Weiss tear, inflammatory polyps, and gastric antral vascular ectasia\textsuperscript{40}; its success is dependent on how “well” the desired lesion is suctioned into the cap opening.

When performing endoscopic mucosal resection (EMR), the use of a cap, commonly referred to as “EMR-C,” is advantageous. During this procedure, the endoscopist presses the cap against the normal mucosa surrounding the target lesion and applies light suction to seal the cap outlet. The snare was then opened and forced to rest along the inner groove of the rim of the cap to form a loop (Fig. 9). The suction was then released, and the cap was used to suck the lesion under a medium to high vacuum. After the endoscopist strangulates the lesion by closing the snare, the suction is again released, allowing the snare to close snugly.\textsuperscript{41} Without suctioning ability from using caps, it would be difficult to ensnare a desired lesion with ease, and it would also be difficult to resect a lesion larger than the diameter of the endoscope. The cap is also useful in retrieving resected specimens.

An over-the-scope clip (OTSC) (Fig. 10) is another therapeutic tool aided by endoscopic caps. The OTSC was developed to compress tissue in the gastrointestinal tract; by grabbing more tissue, they allow for obliteration of arterial blood flow underneath the stigmata of recent hemorrhage. The OTSC is designed to have a transparent cap at the end of the endoscope, on the outside of which lies a detachable clip that looks like a bear claw. Prior to use, the endoscope, aided by a cap, is placed perpendicularly to position the clip immediately above the target lesion as closely as possible. The lesion is aspirated from the inside of the cap, after which the clip is deployed. The four prongs of the clip anchors the lesion from left to right, continuously compressing the tissue. OTSC is not only used as a last resort in unresolved or recurring GI bleeding, but can also be used in other fields of defects, such as perforations and fistulas. In these cases, an anchor (OTSC Anchor; Ovesco Endoscopy AG) or twin grasper (OTSC Twin Grasper; Ovesco Endoscopy AG) is used to better approximate the tissue. Jensen et al.\textsuperscript{42} performed a randomized controlled trial that compared OTSC’s therapeutic effects as an initial treatment for severe non-variceal upper gastrointestinal bleeding. Their results showed that OTSC significantly reduced the rate of further bleeding, regardless of causes, especially in patients with major stigmata of hemorrhage.

**CONCLUSIONS**

This review summarizes the key components that make endoscopic cap an attractive accessory for various procedures. Overall, its application may lead to decreased procedure time, better visualization, and fewer procedural complications; simply put, caps maximize the minimally invasive and prompt potential of endoscopes. Nevertheless, endoscopic caps cannot be reim-

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**Fig. 9.** Single-use distal attachment with rim for performing cap endoscopic mucosal resection (D-402 and D-206; Olympus Co.).

**Fig. 10.** Over-the-scope clip system for applying clips on various lesions in the gastrointestinal tract (OTSC Clip; Ovesco Endoscopy AG).
bursed by Korean Health Insurance, which may preclude their appropriate application.

Conflicts of Interest
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Conceptualization: BIL; Data curation: SK; Formal analysis: all authors; Supervision: BIL; Writing—original draft: SK; Writing—review & editing: all authors.

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REFERENCES
22. Leng Q, Jin HY. Measurement system that improves the accuracy of
24. Ooi M, Young EJ, Nguyen NQ. Effectiveness of a cap-assisted device in the endoscopic removal of food bolus obstruction from the esophagus. Gastrointest Endosc 2018;87:1198–1203.
As how artificial intelligence is revolutionizing endoscopy

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With incessant advances in information technology and its implications in all domains of our lives, artificial intelligence (AI) has emerged as a requirement for improved machine performance. This brings forth the query of how this can benefit endoscopists and improve both diagnostic and therapeutic endoscopy in each part of the gastrointestinal tract. Additionally, it also raises the question of the recent benefits and clinical usefulness of this new technology in daily endoscopic practice. There are two main categories of AI systems: computer-assisted detection (CADE) for lesion detection and computer-assisted diagnosis (CADx) for optical biopsy and lesion characterization. Quality assurance is the next step in the complete monitoring of high-quality colonoscopies. In all cases, computer-aided endoscopy is used, as the overall results rely on the physician. Video capsule endoscopy is a unique example in which a computer operates a device, stores multiple images, and performs an accurate diagnosis. While there are many expectations, we need to standardize and assess various software packages. It is important for healthcare providers to support this new development and make its use an obligation in daily clinical practice. In summary, AI represents a breakthrough in digestive endoscopy. Screening for gastric and colonic cancer detection should be improved, particularly outside expert centers. Prospective and multicenter trials are mandatory before introducing new software into clinical practice.

Keywords: Artificial intelligence; Capsule endoscopy; Digestive endoscopy

INTRODUCTION

With constant advances in information technology and its impact in various aspects of our lives, artificial intelligence (AI) algorithms have emerged to enhance machine performance. Unlike machines, the performance of the human brain could be affected by fatigue, stress, or limited experience. AI technology can compensate for human-limited capabilities, prevent human errors, provide machines with reliable autonomy, and increase the productivity and efficiency of work.

The application of AI technology in gastrointestinal (GI) endoscopy has several advantages. It can reduce the inter-operator variability, improve diagnosis accuracy, and facilitate prompt and precise therapeutic decisions on the spot. Furthermore, AI can reduce the time, cost, and the workload associated with endoscopic procedures. However, the implementation of certain guidelines is required. Different types of AI computer systems exist to fulfil several functions. The two primary categories of AI systems are computer-assisted detection (CADE) for lesion detection and computer-assisted diagnosis (CADx) for optical biopsy and lesion characterization. Other AI systems offer therapeutic assistance, such as lesion delineation for complete endoscopic resection. Computer-aided quality assurance (CAQ) is the ultimate option. This review focuses on the most advanced AI software available in daily clinical practice, and how it will transform our approach (Table 1).
CAPSULE ENDOSCOPY: A FULL AI SYSTEM

Hassan and Haque\(^2\) aimed to draw inferences (bleeding or non-bleeding) using the CADe system by analyzing the spatial domain of an image and extracting features in the frequency domain using complex deep learning (DL). Their goal was to achieve sensitivities and specificities as high as 99% for the detection of GI bleeding. Xiao and Meng\(^3\) developed another CADe system to achieve a 99% F1 score or performance score for GI bleeding detection in wireless capsule endoscopy (WCE). The F1 score was calculated using precision and recall scores. They used DL to build CADe with a dataset consisting of 10,000 WCE images, including 2,850 GI bleeding frames and 7,150 normal frames.

AI systems in video capsule endoscopy were among the first to be used in GI endoscopy, and were mainly used for bleeding detection as CADe. However, the most impressive software was published by Ding et al.\(^4\) with a detailed diagnosis of all small-bowel abnormalities with a specificity and sensitivity well above that of capsule experts. This software had a reading time of 5.9 minutes against 96.2 minutes from the capsule experts. Even more impressively, Zhang et al.\(^5\) developed a gastric magnetically guided capsule with robot for complete gastric diagnosis. This system opens a new era where gastric examination followed by small bowel examination using the same device, with AI for reading.\(^6\) This latest development is turning capsule endoscopy into a full AI diagnosis tool.

HOW DOES AI IMPROVE COLON POLYP DETECTION AND CHARACTERIZATION?

AI for polyp detection and characterization represents the most advanced tool in computer-aided endoscopy, and some of these techniques are already used in daily practice: (1) CADe for polyp detection and identification; (2) CADx for polyp characterization and classification (also called optical biopsy or histology prediction); (3) CADx for the optical characterization of neoplasia in patients with ulcerative colitis (UC); and (4) AI systems can help determine whether additional surgery is needed after endoscopic resection of T1 colorectal cancer by predicting lymph node metastasis.\(^10\)

Since 2022, Mori et al.\(^11\) have developed multiple algorithms designed on an extensive collection of routine colonoscopy videos featuring high-resolution imaging, magnification, and even endocystoscopy. Minute and advanced lesions remain a big challenge, even when we have a chance to undergo high-quality colonoscopy screening. In the realm of AI-medicine, AI for colonoscopy is at the forefront, particularly in the number of randomized controlled trials that have showed its effectiveness in detecting a greater quantity of adenomas.\(^11\) CADe devices have been tested in colonoscopies, increasing the adenoma detection rate (ADR), mainly in Asian populations.\(^12\) Wallace et al.\(^13\) reported a significant improvement in the European population, particularly in the detection of diminutive or flat adenomas. This is especially important since many endoscopists are less experienced in identifying these small lesions compared

<table>
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<tr>
<th>AI system category</th>
<th>Areas of assistance</th>
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<td>Technical Scope guidance for colonoscope insertion</td>
<td>Polyp detection</td>
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<td>Detection (CADe)</td>
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<td>Diagnostic (CADx) Early cancer identification</td>
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<td>Therapeutic Lesion delineation</td>
<td>Assistance in therapeutic decisions</td>
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<td>Capsule endoscopy</td>
<td>Full detailed diagnosis</td>
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AI, artificial intelligence; CADe, computer-assisted detection; CADx, computer-assisted diagnosis.
to their Japanese counterparts. In another study, patients presenting for colorectal cancer screening or surveillance were enrolled across four academic centers in the United States of America (USA). They were randomly assigned to either CADe colonoscopy first or high-definition white-light (HDWL) colonoscopy first, followed immediately by the other procedure, all performed by the same endoscopist in a tandem fashion.\textsuperscript{14} The study cohort included 223 patients and demonstrated a decrease in adenoma and sessile serrated lesion miss rates. There was also an increase in first-pass adenomas per colonoscopy with the use of a CADe system when compared with HDWL colonoscopy alone. Additionally, benefits were observed for proximal colon lesions\textsuperscript{15} and for missing polyps in a large meta-analysis.\textsuperscript{16}

Characterization is another major expected benefit, as routine classifications, such as narrow-band imaging (NBI), International Colorectal Endoscopic, or Japan NBI Expert Team classifications, are not properly applied. Hossain et al.\textsuperscript{17} showed a marked improvement in characterization using AI: CADx with up to 90.9% sensitivity (vs. 48.1% without AI), 95.8% negative predictive value, 80% accuracy with white-light endoscopy, and 84.6% accuracy using image-enhanced endoscopy.

Aside from detection and characterization, other benefits are expected, such as polyp size and histology of colorectal polyps, which are essential factors in appropriate management. However, a query arises regarding how accurately we typically diagnose the polyp size. Most endoscopists would probably not answer this question because they have few opportunities to confirm the accuracy of their own estimations. Kwak et al.\textsuperscript{18} demonstrated the usefulness of a newly developed computer-aided tool based on AI for the accurate measurement of colorectal polyps, even with the pitfalls linked to endoscope handling.

Liu et al.\textsuperscript{14} developed an AI system to measure the fold-examination quality (FEQ) of colonoscopy. The system’s evaluation of FEQ was strongly correlated with FEQ scores from experts, historical ADR, and withdrawal time of each colonoscopist. Other softwares proposed full monitoring: colonic preparation, time to reach the cecum, warning for blind spots, and recording onsite endoscopic report, which is the ultimate goal.\textsuperscript{19}

In summary, CADe should be used worldwide for screening colonoscopies based on the World Endoscopy Organization position statement:\textsuperscript{20} (1) CADe for colorectal polyps is likely to improve the effectiveness of colonoscopy by reducing the adenoma miss rates, thereby increasing adenoma detection. (2) In the short-term, the use of CADe is likely to increase the healthcare costs by detecting more adenomas. (3) In the long-term, the increased cost of CADe could be balanced by savings in costs related to cancer treatment (surgery, chemotherapy, or palliative care) owing to CADe-related cancer prevention. (4) Healthcare delivery systems and authorities should evaluate the cost-effectiveness of CADe in order to support its use in clinical practice. (5) CADx for diminutive polyps (≤5 mm), when it has sufficient accuracy, is expected to reduce the healthcare costs by reducing the number of unnecessary polypectomies, pathological examinations, or both. As a significant number of hyperplastic polyps are removed, the discard policy allows the resection of benign adenomas without further costly pathological examinations.\textsuperscript{21}

**HOW AI IMPROVE EARLY GASTRIC CANCER DETECTION AND MANAGEMENT?**

Early detection is essential for improving the prognosis and mortality of gastric cancer, particularly in countries with high incidence. Early detection also allows for minimally invasive endoscopic resection, which has been shown to have excellent overall survival comparable to gastrectomy, while preserving stomach function. Without AI, the false-negative rates of gastric cancer during screening endoscopy range from 4.6% to 25.8%. Multiple studies have demonstrated the benefits of AI for detection and characterization (assessing the depth of invasion) based on Japanese classifications, detecting *Helicobacter pylori* infection, and making endoscopic resection more accurately with delineation of the cancer area.\textsuperscript{22}

Ishioka et al.\textsuperscript{23} developed an artificial diagnostic support tool, ‘Tango’, to differentiate early gastric cancers (EGCs) using still images of 150 neoplastic and 165 non-neoplastic lesions. Tango achieved superiority over the specialist based on sensitivity (84.7% vs. 65.8%; difference, 18.9%; 95% confidence interval [CI], 12.3%–25.3%) and demonstrated non-inferiority based on accuracy (70.8% vs. 67.4%). More importantly, in clinical practice, Tango achieved superiority over the non-specialist based on sensitivity (84.7% vs. 51.0%) and accuracy (70.8% vs. 58.4%). With the same goal, Wu et al.\textsuperscript{24} reported a prospective study that included 1,050 patients using ENDOANGEL software (Jinshan) for the detection of EGC and monitoring the quality of gastric examination. The ENDOANGEL group had fewer blind spots (5.38 vs. 9.32, p<0.001) and detected 196 lesions and three EGCs with a per-lesion accuracy of 84.7%, sensitivity of 100%, and specificity of 84.4% for detecting gastric cancer. Similarly, intestinal metaplasia detection is improved by AI.\textsuperscript{25}
CADx for gastroscopy is expected to serve as a second observer during real-time gastroscopy, helping endoscopists detect more neoplasms. Simultaneously, it serves as an educational tool for training novice endoscopists.

**AI FOR ESOPHAGEAL DISEASES**

Esophageal cancer (EC) is a common and severe disease worldwide. Although the morbidity associated with esophageal squamous cell carcinoma has decreased in recent years, it remains the predominant histological type of EC in some regions (Asia and Africa). Most patients are diagnosed at advanced stages of the disease. Therefore, early detection is crucial to improve treatment and survival. High-resolution endoscopy with NBI and magnification is the standard for detection and characterization.

Everson et al. demonstrated the benefit of AI in a panel of both European and Asian endoscopists compared with the goal standard, even with different pathological assessments in different areas, but based on intrapapillary capillary loop endoscopic classification. Expert European and Asian endoscopists attained F1 scores (a measure of binary classification accuracy) of 97.0% and 98%, respectively. The sensitivity and accuracy of the European and Asian clinicians were 97%, 98%, 96.9%, and 97.1%, respectively. However, even more importantly, Yuan et al. reported the benefit of AI in obtaining better delineation. Non-magnified NBI images (10,047 still pictures and 140 videos from 1,120 patients and 1,183 lesions) from four hospitals were collected and annotated. The delineation performance of the system was compared with that of the endoscopists. Furthermore, the system was directly integrated into the endoscopy equipment, and its real-time diagnostic capability was prospectively estimated. The accuracy was 91.4% for detecting lesions and 85.9% for delineating lesions. As expected, the benefit was superior to that of junior doctors and similar to that of experts.

In Western countries, esophageal adenocarcinoma has been linked with Barrett’s esophagus (BE). The prognosis is strongly related to the stage of diagnosis. However, >40% of patients are diagnosed after the disease has metastasized, with a survival rate of <20%. Adenocarcinomas in BE patients are often preceded by high-grade dysplasia. Patients with BE undergo regular surveillance to detect neoplasia at an early stage, and can be treated with endoscopic resection. Detailed characterization requires expertise or AI. Abdelrahim et al. carried out a multicenter study for the detection and localization of Barrett’s neoplasia and assessed its performance compared with that of general endoscopists by using real-time video sequences. The CADx system detected Barrett’s neoplasia with a sensitivity, specificity, negative predictive value, and accuracy of 93.8%, 90.7%, 95.1%, and 92.0%, respectively, compared with the endoscopists’ performance of 63.5%, 77.9%, 74.2%, and 71.8%, respectively (p<0.05 in all parameters). The CADx system localized neoplastic lesions with an accuracy, mean precision, and mean intersection over union of 100%, 0.62, and 0.54, respectively. This promising result for the common situation in Europe and USA should be tested in prospective clinical trials.

**PROMISING DEVELOPMENTS**

Inflammatory bowel diseases, such as UC and Crohn’s disease, are chronic conditions for which endoscopic diagnosis and assessment require considerable clinical expertise. A future benefit will be the introduction of AI in clinical trials in a group of patients. This will help prevent clinical bias and eliminate interobserver variation. In summary, I agree with Murino and Rimondi, “AI is going to drastically change our approach to diagnosis endoscopy. In contrast to its human counterpart, AI can manage an exceptional amount of data simultaneously, does not get fatigued, and can be highly effective and efficient”, especially in patients with small-bowel disease. At present, with respect to endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography, AI softwares are at an early stage. In the future, AI software will be developed for quality assurance, monitoring colonoscopy, and producing immediate onsite endoscopic reports. This represents a significant potential improvement in daily practice, particularly for non-expert units.

**DRAWBACKS**

As medical knowledge progresses, the use of generative AI in practice depends on its ability to provide up-to-date information. Although these tools can access the most recent data, their ability to convey and account for data that change over time remains unclear. Similarly, there is a need to clarify data originating from various sources, including differentiating between established clinical standards and emerging research. This complexity is compounded in situations where multiple current resources may not be in agreement (e.g., different guidelines on colorectal cancer screening). To accept AI algorithms in clinical practice, their effectiveness, clinical value, and reliability must...
be rigorously assessed. Parasa et al.\textsuperscript{1} provided a guiding framework for all stakeholders in endoscopy. At present, there is no AI ecosystem regarding the standards, metrics, and evaluation methods for emerging and existing AI applications to aid in their clinical adoption and implementation. They also provide guidance and best practices for the evolution of AI technologies as they mature in the endoscopy space. The model cart for AI in endoscopy includes multiple groups of features: basic information about the model, product details, clinical implications, performance evaluation, explainable/trustworthy AI, model development facts, and postmarked/real-world data aside from all factors. It is critical in clinical practice to avoid a multitude of false alert-disturbing endoscopic examinations. This American Society for Gastrointestinal Endoscopy (ASGE) technical document is important for all AI developers. If CADe is effective, it remains to be understood why its adoption in clinical practice appears to be progressing slowly. The drawbacks are mainly related to costs (without healthcare system reimbursement), and products are commercially available without proper evaluation. Excessive false positive results disrupt the endoscopist’s attention and can affect the overall results. For colorectal cancer screening, an increase in ADR has proved to decrease the post-colonoscopy cancer risk, but not yet with an AI-associated gain.\textsuperscript{8} The resect-and-discard strategy based on characterization and expected histology is still a subject of debate in several countries outside USA and could confuse many endoscopists.\textsuperscript{35} Developers should follow the recent guidelines from ASGE in all cases.\textsuperscript{1}

\section*{ACCESSIBILITY}

At the fundamental level, these models are trained on a breadth of data beyond those accessible to most individuals and require accurate databases.\textsuperscript{36} The synthesis of this information presents an opportunity to broaden access and may aid in reducing disparities in underserved communities. However, this information alone provides little utility if it cannot be understood. Health literacy remains a barrier in providing usable responses to complex health-related questions. The response readability of ChatGPT exceeded the 8th-grade level, limiting its utility for a subset of patients and potentially widening the gap in healthcare access.\textsuperscript{37}

\section*{CONCLUSIONS}

I believe that the future of GI endoscopy will undergo dramatic transformation in the upcoming years with the integration of AI into this field (Table 2). Manufacturers have made huge investments in this promising technology, and the results have started to emerge. Currently, endoscopists are responsible for performing, detecting, analyzing, and providing treatment independently. In addition, they must possess extensive experience and enormous knowledge to offer the best care to their patients. They have to maintain good memory and practical skills over time while staying updated on every new piece of information, recommendation, and guideline.

\textbf{Conflicts of Interest}

The author has no potential conflicts of interest.

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\section*{REFERENCES}


\begin{table}[h]
\centering
\begin{tabular}{|c|p{8cm}|}
\hline
\textbf{Step} & \textbf{Development} \\
\hline
1 & Software conception  \\
& What software can do  \\
& How it will perform  \\
& Quality of endoscopic material (still pictures, recorded videos)  \\
\hline
2 & During endoscopic procedures  \\
& Reduced false alarm and operator distraction  \\
& Clear explanation of system performance  \\
\hline
3 & Post-market evaluation  \\
& Accurate analysis of software performance  \\
& Practitioner feedback  \\
\hline
4 & Immediate and corrected new update version  \\
\hline
\end{tabular}
\caption{Steps for how AI will revolutionize endoscopy}
\end{table}


30. Murino A, Rimondi A. Automated artificial intelligence scoring systems for the endoscopic assessment of ulcerative colitis: how far are we from clinical application? Gastrointest Endosc 2023;97:347–349.


Role of endoscopic duodenojejunal bypass liner in obesity management and glycemic control

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The treatment of obesity and its comorbidities ranges from clinical management involving lifestyle changes and medications to bariatric and metabolic surgery. Various endoscopic bariatric and metabolic therapies recently emerged to address an important therapeutic gap by offering a less invasive alternative to surgery that is more effective than conservative therapies. This article comprehensively reviews the technical aspects, mechanism of action, outcomes, and future perspectives of one of the most promising endoscopic bariatric and metabolic therapies, named duodenojejunal bypass liner. The duodenojejunal bypass liner mimics the mechanism of Roux-en-Y gastric bypass by preventing food contact with the duodenum and proximal jejunum, thereby initiating a series of hormonal changes that lead to delayed gastric emptying and malabsorptive effects. These physiological changes result in significant weight loss and improved metabolic control, leading to better glycemic levels, preventing dyslipidemia and non-alcoholic fatty liver disease, and mitigating cardiovascular risk. However, concern exists regarding the safety profile of this device due to the reported high rates of severe adverse events, particularly liver abscesses. Ongoing technical changes aiming to reduce adverse events are being evaluated in clinical trials and may provide more reliable data to support its routine use in clinical practice.

Keywords: Bariatric surgery; Diabetes mellitus, type 2; Endoscopy; Gastrointestinal disorders; Obesity

INTRODUCTION

Obesity has reached pandemic proportions, with estimates suggesting that by 2035, 51% of the population will be overweight or obese. This escalating crisis comes at a staggering cost of 4 trillion US dollars, encompassing diminished productivity, premature mortality, and increased direct healthcare expenditures. Obesity is intricately linked with a range of comorbidities, including dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, and others. Notably, among these conditions, type 2 diabetes mellitus (T2DM) stands out prominently. The profound correlation between obesity and T2DM has led to the conceptualization of the term “diabesity.”

Bariatric surgery is currently the most effective and durable treatment for obesity and its associated comorbidities. However, <2% of eligible patients undergo bariatric surgery for a variety of reasons, including surgical risk, personal preference, cost, and access. Initial approaches to managing obesity and its related comorbidities involve lifestyle modifications encompassing diet and exercise. Additionally, the use of weight loss medications is increasing due to the higher efficacy than previously available medications. However, poor long-term...
weight loss, especially after medication discontinuation, often necessitates further therapeutic intervention. Consequently, endoscopic bariatric and metabolic therapies (EBMTs) have emerged as an alternative for patients with obesity, including those who are ineligible or reluctant to undergo bariatric and metabolic surgical intervention.\textsuperscript{3,7}

The duodenojejunal bypass liner (DJBL) (EndoBarrier; GI Dynamics) (Fig. 1) is a minimally invasive and fully reversible procedure that emulates the metabolic effects of Roux-en-Y gastric bypass (RYGB) by preventing food contact with the duodenum and proximal jejunum, thereby initiating a series of hormonal changes that lead to delayed gastric emptying and malabsorptive effects. These physiological changes result in significant weight loss and improved metabolic control, leading to better glycemic levels, preventing dyslipidemia and NAFLD, and mitigating cardiovascular risk. However, concern exists regarding the device’s safety profile due to the reported high rates of severe adverse events (SAEs).\textsuperscript{7} To increase our understanding of the role of DJBL in the management of obesity and its related comorbidities, this article comprehensively reviews its technical aspects, mechanism of action, outcomes, and future perspectives.

DEVICE CHARACTERISTICS AND ENDOSCOPIC PLACEMENT/REMOVAL

The DJBL is a single-use endoscopic device composed of a 60-cm impermeable fluoropolymer liner and a nitinol anchor that enables its fixation in the duodenal bulb. This liner impedes the mixing of chyme with bile and pancreatic secretions prior to the proximal portion of the jejunum.

The DJBL is placed endoscopically under general anesthesia. First, a guidewire is positioned in the jejunum (as distally as possible) and the device is placed over the guidewire under fluoroscopic and endoscopic assistance. The fluorine polymer liner is then advanced to overlay the duodenum and the proximal jejunum. After the appropriate position is confirmed on fluoroscopy, the anchoring system is deployed and fixed at the duodenal bulb (Fig. 2). Finally, a water-soluble contrast is injected through the working channel to ensure proper device placement.

![Photograph of the duodenojejunal bypass liner.](image1)

![Photographs of step by step duodenojejunal bypass liner (DJBL) placement process.](image2)

**Fig. 1.** Photograph of the duodenojejunal bypass liner.

**Fig. 2.** Photographs of step by step duodenojejunal bypass liner (DJBL) placement process. (A) Endoscopic evaluation followed by distal guidewire placement. (B) DJBL placement over the guidewire. (C) Anchor system deployment in the duodenal bulb. (D) Final appearance after successful DJBL placement.
position and the absence of liner obstructions (“kinks”).

The endoscopic removal of the DJBL should be performed under general anesthesia and fluoroscopic assistance utilizing a device-specific grasping tool within a suitable foreign body hood (similar to a large cap) positioned at the distal end of the gastroscope. The device is ideally removed within 12 months unless early removal is required due to an adverse event. A prior study reveal that DJBL use longer than 12 months (up to 24 months) increases the risk of adverse events without providing clinical benefits.

**PHYSIOLOGICAL ASPECTS/MECHANISM OF ACTION**

EBMTs are generally classified into four categories: space occupying, gastric remodeling, aspiration therapy, and small bowel therapies. The DJBL is categorized as a small bowel therapy that aims to replicate the mechanisms of action of RYGB, a surgery recognized for its significant metabolic effects.

Among its mechanisms of action, the incretin effect is specifically relevant. Incretins are gut hormones that enhance insulin secretion following food consumption. The main incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP is secreted by K enteroendocrine cells in the duodenum and proximal jejunum upon contact with food, thus stimulating insulin synthesis and secretion. Nevertheless, this process may contribute to the onset of T2DM. Conversely, GLP-1 acts in the distal small intestine, stimulating beta cell proliferation, promoting insulin production and secretion, inhibiting glucagon secretion, slowing peristalsis, and promoting satiety.

Another crucial hormonal effect of DJBL is linked to gastric emptying. Ghrelin, a hormone produced in the gastric fundus and pancreas, stimulates hunger. Conversely, peptide YY (PYY) inhibits gastrointestinal emptying and enhances satiety.

By preventing food contact with the mucosa of the duodenum and proximal jejunum, DJBL reduces the anti-incretin effect, subsequently improving insulin resistance and glucose regulation. Additionally, the presence of undigested food in the distal portions of the small intestine stimulates incretin secretion and insulin production and enhances glycemic homeostasis.

A previous meta-analysis demonstrated that, upon device removal, postprandial GLP-1 levels significantly increase and GIP levels decrease compared to baseline values. The same study also evidenced a notable increase in fasting ghrelin and PYY levels.

A comprehensive analysis of the mechanisms of action revealed comparable effects of DJBL and RYGB. Overall, both strategies elevate GLP-1 and PYY levels while reducing GIP concentrations. Moreover, both methods mechanically exclude the duodenum and proximal jejunum, exposing the distal segments of the small intestine to undigested contents. Divergent findings have emerged concerning the effects on ghrelin; its levels decrease with RYGB but increase with the DJBL. The surgical approach also involves isolation of the cardia, a partial vagotomy, and exclusion of the distal stomach, while the DJBL delays gastric emptying.

**CLINICAL OUTCOMES**

**Weight loss**

A recent systematic review and meta-analysis examined the impact of DJBL on weight loss and glycated hemoglobin (HbA1c) levels. The meta-analysis included 10 randomized controlled trials (evidence 1A) examining a total of 681 patients (80% with T2DM) who underwent device placement along with 291 controls. The percentage excess weight loss (%EWL) was higher in the DJBL than control group (mean difference [MD], +11.39% [+7.75 to +15.03%]; p<0.00001, I²=91%) as well as absolute weight loss (AWL) and total weight loss (%TWL), with MD values of +6.64 kg [+4.77 to +8.50 kg], p<0.00001, I²=98% and +4.43% [+1.95 to +6.90%], p=0.0005, I²=98%, respectively, compared with other weight loss modalities such as aspiration therapy and intragastric balloon.

All EBMTs carry the risk of weight regain after their removal. In a retrospective study, a follow-up assessment performed 6 months after DJBL removal showed that 66.7% of patients with class I obesity (at baseline) maintained a stable weight or regained only <7%. In contrast, no patients with a body mass index (BMI) >35 kg/m² (at baseline) were able to maintain or present a weight regain <7%. A study evaluated the outcomes at 4 years after DJBL explantation and showed improvement in AWL, %TWL, and BMI. However, none of these parameters were significantly different compared to baseline. Thus, the effect of initial DJBL treatment on weight reduction seemed diminished after long-term follow-up. However, larger prospective studies with long-term follow-up periods are needed to clarify its long-term effects.
Metabolic improvement

As previously emphasized, due to mechanisms akin to RYGB, the DJBL is anticipated to yield significant effects on glycemic control. Notable reductions in HbA1c levels have been demonstrated as in a recent level 1A evidence study, with an MD of \(-1.03\) (\(-1.56\) to \(-0.50\), \(p=0.0001\), \(F=65\%\)).\(^{18}\) Within the Worldwide Endobarrier Registry established by the Association of British Clinical Diabetologists, 1,022 patients from 34 centers in 10 countries were registered through October 2022. The registry revealed considerable improvements in weight loss, systolic blood pressure, cholesterol levels, and HbA1c, with more pronounced enhancements observed in patients with higher BMI and HbA1c levels. Notably, there was a reduction of \(-1.3\pm1.5\) in HbA1c (\(p<0.0001\)).\(^{23}\)

A recent study examined the metabolic effects of DJBL in patients with NAFLD. Over a 48-week duration, 31 patients with obesity and T2DM exhibited a reduction in steatosis and a decreased risk of developing non-alcoholic steatohepatitis, although the impact on hepatic fibrosis was limited.\(^{34}\) Another study assessed 71 patients who underwent DJBL treatment for 9-12 months, followed by a 6-month follow-up after its removal. This study demonstrated a decrease in the fatty liver index during its use (93.38 vs. 98.22, \(p<0.001\)) along with reductions in alanine aminotransferase (29.03 vs. 42.29 U/L, \(p<0.0001\)) and cytokeratin-18 fragments (190.6 vs. 276 U/L, \(p<0.0001\)), which remained stable in the following 6 months.\(^{25}\)

Moreover, a relatively unexplored undesired effect of the DJBL involves vitamin and mineral malabsorption. An analysis of 19 insulin-dependent diabetes patients after 12 months of treatment observed significant decreases in hemoglobin, hematocrit, iron, ferritin, vitamin B\(_{12}\), albumin, and pre-albumin. While no substantial changes in bone mineral density were noted, further research is needed to formulate nutritional recommendations for these patients.\(^{26}\)

As a result of enhanced metabolic control, a prospective study of 71 patients indicated a relative risk reduction of cardiovascular events over a 4-year period among patients undergoing DJBL treatment. The risk reduction reached 16.2\% at the time of its removal, and the benefits persisted for 6 months thereafter.\(^{27}\)

Safety

In a previous systematic review\(^{28}\) considering the American Society for Gastrointestinal Endoscopy (ASGE) grading system,\(^{29}\) the rate of DJBL-related adverse events was 84.4\%, with 75.8\% classified as mild and 3.7\% as severe.\(^{28,29}\) In a more recent meta-analysis,\(^{30}\) SAEs occurred in 19.7\% of patients according to the Clavien-Dindo\(^{30}\) and AGREE\(^{31}\) classifications. The majority of adverse events—predominantly those involving abdominal pain and nausea—are linked to the initial adaptation period after device. Within the Worldwide DJBL Registry, 4.2\% of patients reportedly experienced SAEs, notably bleeding (2.3\%), hepatic abscesses (1.1\%), and pancreatitis/cholecystitis (0.4\%).\(^{32}\)

While most SAEs can be managed through endoscopic removal of the DJBL,\(^{18,32}\) in 2015, the US Food and Drug Administration (FDA) halted the ENDO trial (NCT01728116) due to the risk of device-related hepatic abscesses.\(^{33}\) To overcome this issue, the company is implementing technical modifications and recommending the discontinuation of proton pump inhibitor intake during DJBL use.

COMPARISON WITH OTHER METHODS

Compared to RYGB, despite their physiological similarities, the surgical approach leads to more significant weight loss. In a propensity match score study comparing RYGB and DJBL with a 12-month follow-up, the mean BMI reduction (11.54±4.47 kg/m\(^2\) vs. 6.23±2.36), %TWL (27.93±8.57\% vs. 15.04±5.73), and %EWL (67.26±24.6\% vs. 44.48±27.07) were higher in the RYGB group. In terms of metabolic effects, at 1 year of follow-up, glycemic control had improved significantly in both groups with no significant intergroup difference.\(^{34}\)

Current FDA-approved EBMTs include intragastric balloon, aspiration therapy, and gastric remodeling therapies such as endoscopic sleeve gastropasty with the Apollo Overstitch suturing device (Apollo Endosurgery Inc.) as well as gastric suturing using the Endomina platform (Endo Tools Therapeutics S.A.).\(^{13}\) The ASGE/American Society for Metabolic and Bariatric Surgery (ASMB) criteria for adopting EBMTs in clinical practice encompass a %EWL ≥25\% versus the control group and an SAE rate ≤5\%.\(^{34,35}\) Therefore, the available data demonstrate that the DJBL does not achieve the ASGE/ASMBS criteria for adoption in clinical practice. More data are expected to be obtained from the ongoing STEP-1 trial (NCT04101669), which was initiated in 2019 and is expected to end in 2025.\(^{36}\)

Among the most commonly used EBMTs (Table 1),\(^{18,19,37-41}\) two directly target the small bowel as the DJBL and the duodenal mucosal resurfacing (DMR). While no EBMTs targeting the small bowel have been approved to date by the FDA for routine practice,\(^{42}\) the initial data are promising.
Table 1. Summary of characteristics of the various EBMTs

<table>
<thead>
<tr>
<th>EBMTs</th>
<th>Mechanism of action</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>% TWL</th>
<th>% EWL</th>
<th>% SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DJBL</td>
<td>Prevents food contact with the duodenum and proximal jejunal mucosa</td>
<td>Reversible</td>
<td>Short duration of treatment (removed within 6–12 mo)</td>
<td>4.43</td>
<td>11.4</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effective in T2DM control</td>
<td>Poor safety profile</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Considerable weight loss</td>
<td>Non-FDA approved</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Need fluoroscopic assistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGB</td>
<td>Mechanical &quot;obstruction&quot; of the stomach (space occupying device)</td>
<td>Reversible</td>
<td>Significant weight regain after removal, short duration of treatment (6–12 mo)</td>
<td>12.1</td>
<td>34.8</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Delay gastric emptying</td>
<td>Different models commercially available</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA approved</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Widely available</td>
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<tr>
<td>Gastric remodeling</td>
<td>Reduction of the stomach by full-thickness sutures of the gastric body</td>
<td>2-Years weight loss maintenance</td>
<td>Double-channel endoscope is required with the most used system (Overstitch; Apollo Endosurgery Inc.). However, a single channel device is now available (Overstitch Sx).</td>
<td>15.34</td>
<td>55.6</td>
<td>2.8</td>
</tr>
<tr>
<td>ESG</td>
<td>Delay gastric emptying</td>
<td>FDA-approved</td>
<td>Lower weight loss compared to other gastric remodeling techniques</td>
<td>11.8</td>
<td>45.1</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT data supporting its use</td>
<td>Non-reversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo-DIVA</td>
<td>Reduction of the stomach by full-thickness sutures of the gastric body</td>
<td>Appears to be more durable than other remodeling techniques</td>
<td>Single channel scope and ultra-slim scope are required.</td>
<td>12.68</td>
<td>48.86</td>
<td>2.84</td>
</tr>
<tr>
<td></td>
<td>Delay gastric emptying</td>
<td></td>
<td></td>
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<tr>
<td>POSE-2</td>
<td>Reduction of the stomach by full-thickness plications of the gastric body</td>
<td>Sustained long-term weight loss during its use</td>
<td>Complications similar to percutaneous endoscopic gastrostomy, such as granulation tissue formation, and buried-bumper syndrome Gastrocutaneous fistula is common when used for more than 3 years.</td>
<td>17.8</td>
<td>46.3</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Delay gastric emptying</td>
<td>Reversible</td>
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<tr>
<td></td>
<td></td>
<td>FDA-approved</td>
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<tr>
<td>Aspiration therapy</td>
<td>Aspiration of undigested food from the stomach after eating</td>
<td>Sustained long-term weight loss during its use</td>
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<tr>
<td></td>
<td></td>
<td>Reversible</td>
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<tr>
<td></td>
<td></td>
<td>FDA-approved</td>
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<tr>
<td>DMR</td>
<td>Ablation of the duodenal mucosa</td>
<td>Promising results in terms of glycemic control and improvements in liver parameters in patients with NAFLD</td>
<td>Not effective for weight loss</td>
<td>Not significant</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Not widely available</td>
<td>Not significant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Non-FDA approved</td>
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</tbody>
</table>

EBMT, endoscopic bariatric and metabolic therapy; TWL, total weight loss; EWL, excess weight loss; SAE, severe adverse event; DJBL, duodenaljejunal bypass liner; T2DM, type 2 diabetes mellitus; IGB, intragastric balloon; FDA, Food and Drug Administration; ESG, endoscopic sleeve gastroplasty; RCT, randomized controlled trial; POSE, primary obesity surgery endoluminal; DMR, duodenal mucosal resurfacing; NAFLD, non-alcoholic fatty liver disease.

The DMR involves thermal ablation of the duodenal mucosa that aims to enhance glycemic control in patients with T2DM. A meta-analysis of four studies including 127 patients demonstrated reductions in HbA1c by 1.72% and 0.94% at 3 and 6 months of follow-up, respectively. This improvement was accompanied by improved hepatic function markers such as alanine aminotransferase. Interestingly, DMR did not influence weight loss. These findings suggest that DMR could be an
option for achieving at least short-term glycemic control and managing hepatic steatosis in non-insulin-dependent T2DM patients. Thus, the limited effect on weight loss of DMR seems to favor the use of DJBL in patients with both T2DM and overweight/obesity.

Among the various EBMTs, device selection must consider several factors such as personal and local experience, device availability, patient preference, and cost.

**FUTURE PERSPECTIVES**

As the EBMT field evolves, several areas must be addressed to optimize outcomes. Patient selection is key to achieving better outcomes. Several factors that may interfere in the mechanism of action of EBMTs are being investigated, such as gastric motility, bile acid metabolism, the gut microbiome, enteral hormones, and genetics. The combined use of two EBMT devices, applied simultaneously or sequentially, as well as that of an EBMT with weight loss medications, appear to improve efficacy and are under investigation. As any other medical treatment, a great doctor-patient relationship is crucial to achieving satisfactory outcomes, including close follow-up with a multidisciplinary team.

Larger randomized controlled trials with long-term follow-up are still required to gather more robust evidence for EBMT utilization, mainly therapies targeting the small bowel such as the DJBL.

**CONCLUSIONS**

Although the ASGE/ASMBS thresholds for the adoption of DJBL in the endoscopic management of obesity was not reached by studies to date, the DJBL may still play a role in the management of obesity and T2DM. DJBL is a minimally invasive therapy with higher efficacy than control groups in high-quality comparative studies. Safety remains a concern due to its non-negligible rate of SAEs. Therefore, the device requires modification with the aim of improving its safety profile. Additionally, standardized training is needed to enhance outcomes and facilitate its broad adoption. As an EBMT, the DJBL may become an important tool in the armamentarium for the battle against the diabesity pandemic.

**Conflicts of Interest**

Diogo Turiani Hourneaux de Moura is currently serving as an associate editor for *Clinical Endoscopy*; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. Diogo Turiani Hourneaux de Moura reports receiving personal fees from Bariatek-Advanced Bariatric Solutions outside the submitted work. The other authors have no potential conflicts of interest.

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**Author Contributions**

Conceptualization: DTHM; Project administration: DTHM; Supervision: all authors; Validation: all authors; Writing—original draft: WFI, VldO; Writing—review & editing: all authors.

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**REFERENCES**


36. Mauro A, Lusetti F, Scalvini D, et al. A comprehensive review on bariatric endoscopy: where we are now and where we are going. Medicina (Kaunas) 2023;59:636.


Efficacy and safety of endoscopic submucosal dissection for colorectal dysplasia in patients with inflammatory bowel disease: a systematic review and meta-analysis

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Efficacy and safety of endoscopic submucosal dissection for colorectal dysplasia in patients with inflammatory bowel disease: a systematic review and meta-analysis

ESD is safe and effective for the resection of dysplastic lesions in IBD with excellent pooled rates of en-bloc and R0 resection.

12 Studies
291 Dysplastic lesions
274 IBD patients

- En-bloc resection rate 92.5% (95% CI 87.9–95.4)
- R0 resection rate 81.5% (95% CI 72.5–88)
- Local recurrence rate 3.9% (95% CI 2–7.5)
- Bleeding rate 7.7% (95% CI 4.5–13)
- Perforation rate 5.3% (95% CI 3.1–8.9)

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), is associated with an increased risk of colorectal cancer (CRC), especially in patients with extensive inflammation and longer disease duration without remission. Frequent screening colonoscopy and surveillance of colorectal dysplasia in patients with IBD have demonstrated a decreased risk of advanced and interval CRC. However, this entirely depends on identifying and effectively resecting the colorectal dysplasia.

Endoscopic removal of dysplastic lesions by endoscopic submucosal resection (EMR) and endoscopic submucosal dissection (ESD) in IBD can be challenging because of chronic inflammation and extensive submucosal fibrosis. In the past, dysplasia in IBD was managed by surgical resection; however, the emergence of endoscopic resection has reduced the need for surgical intervention. Current guidelines recommend surgery to be reserved for endoscopically unresectable and invisible high-grade dysplasia in IBD. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines and the Surveillance for Colorectal Dysplasia in IBD recommend endoscopic resection of visible dysplastic lesions with distinct borders and absence of submucosal invasion.

EMR may not be effective for large dysplastic lesions (>2 cm), especially with the presence of submucosal invasion or friable mucosa. The ESD technique overcomes the limitations of EMR for dysplastic lesions in IBD by allowing en-bloc resection of lesions, regardless of size and presence of submucosal fibrosis. It facilitates detailed histological examination of the resected lesion and significantly reduces the risk of recurrence.

Evidence regarding the outcomes of ESD for colorectal dysplasia in IBD is limited to smaller retrospective, single-center studies. We conducted this meta-analysis to appraise the current literature regarding the safety and efficacy of ESD for colorectal dysplasia in IBD.

METHODS

Search strategy

Multiple databases, including PubMed, Scopus, Embase, and Cochrane, were comprehensively searched from their inception until October 2022. The search was limited to studies in the English language only, and animal studies were excluded. The search strategy was designed and conducted by an experienced librarian with input from the study’s principal investigator. Keywords and controlled vocabulary were used to search for studies on ESD in patients with IBD. The full literature search strategy is provided in Supplementary Material 1. Reference lists of articles were analyzed to identify studies missed on the initial search. Preferred reporting items in meta-analysis, and meta-analysis of observational studies checklists were followed, and are summarized in Supplementary Materials 2 and 3.

Study selection

Studies reporting outcomes of ESD for colorectal dysplasia in patients with IBD; comprising UC, CD, or both UC and CD; and with appropriate data including resection and adverse event rate regardless of study setting, geographical location, or...
follow-up period were included.

Studies were excluded based on the following criteria: (1) involving animal subjects, (2) involving patients aged <18 years, (3) not published in the English language, (4) involving hybrid ESD, (5) with a sample size of less than five, and (6) not published as full manuscripts (abstract or conference proceedings). Two reviewers carefully reviewed each study for eligibility based on the above-mentioned criteria. The authors were contacted by e-mail for any clarifications regarding study data.

Data extraction
Data extraction was performed by two reviewers (TFM and VS), and a third author analyzed the data (BPM). Data regarding study and patient characteristics and outcomes were extracted onto a standardized form. In case of any discrepancy, a consensus was achieved by discussion with the senior author (GSK). Authors of the included studies were contacted by e-mail if further information on study data was needed.

Outcome assessment
We assessed the following outcomes: pooled rates of en-bloc resection, R0 resection, curative resection, adverse events (bleeding and perforation), local and metachronous recurrence, and additional surgery after ESD. Based on data availability and feasibility, predetermined subgroup analyses were planned based on the IBD type (UC, CD, and UC+CD), study sample size (<20 or >20), and geography (United States [US], Asia, and others). Meta-regression was planned based on lesion location (right or left), morphology (polypoid or nonpolypoid), lesion border (distinct or indistinct), and surrounding mucosa (remission or active) to assess potential causes of heterogeneity and predictors of clinical outcomes.

1) Assessment of methodology and definitions
The quality of each study was assessed using the Newcastle-Ottawa scale for cohort studies.14 Two authors assessed and scored each study independently (TFM and VS). Details of the individual study scoring are provided in Supplementary Table 1.

Data on resection, recurrence, and adverse event rates were collected from the original studies. En-bloc resection was defined as the complete removal of the lesion in one piece. The pooled rate of R0 resection was defined as the complete removal of the lesion with negative histological margins. Variability was observed with the definition of ‘curative resection’. The most consistent definition for ‘curative resection’ was when pathological findings revealed R0 resection without any of the following features: submucosal deep invasion (≥1,000 μm), lymphovascular involvement, or poorly differentiated adenocarcinoma component. Bleeding and perforation events, as reported in the original studies, were considered adverse events. Local recurrence was defined as the presence of dysplastic lesion at the resection site during follow-up colonoscopy. Metachronous tumor was defined as a new lesion detected in a colorectal area, other than the primary lesion site, more than six months following ESD.

Statistical analysis
We used meta-analysis techniques, particularly the random-effects model, to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird. When the incidence of an outcome was zero in a study, a continuity correction of 0.01 was added to the number of incident cases before statistical analysis. Pooled proportions with corresponding 95% confidence intervals (CIs) were calculated for categorical outcomes, and pooled mean differences were calculated for continuous outcomes. We assessed heterogeneity between study-specific estimates using the Cochran Q statistical test for heterogeneity; 95% prediction interval (PI), which deals with the dispersion of the effects; and I² statistics. We considered values of <30%, 30% to 60%, 61% to 75%, and >75% to indicate low, moderate, substantial, and considerable heterogeneity, respectively. Publication bias was ascertained qualitatively via visual inspection of the funnel plot and quantitatively using the Egger test. All analyses were performed using the Comprehensive Meta-Analysis (CMA) software ver. 4 (BioStat).

RESULTS
Search results and population characteristics
The initial search generated 103 studies, of which 47 duplicates were removed and 56 studies were screened and fully assessed. Twelve studies were included in the final analysis.15-26 The schematic flow diagram for the study selection process is illustrated in Supplementary Figure 1.

A total of 291 dysplastic lesions were removed by ESD in 274 patients. The median age was 62 years (interquartile range, 54–65). Of the patients, 56% were male (n=167), and 44% were female (n=132). The mean lesion size was 28.6 (18.3–40.7) mm. Approximately 77.3% of lesions were in the left colon (n=184), 80.7% were nonpolypoid (n=192), and 73.2% had submucosal
fibrosis \( (n=161) \). The overall mean procedure time was 72.7 (95% CI, 53.2–92.2) minutes (Supplementary Fig. 2). The median study follow-up time was 25 months. Further study and baseline patient characteristics and study outcomes are summarized in Tables 1 and 2, respectively.15–26

**Characteristics and quality of included studies**

Three studies were prospectively conducted,16,17,21 and five studies were multicenter studies.15,18,21,23,25 The assessment of study quality is detailed in Supplementary Table 1. Overall, two studies were considered high quality, and ten studies were medium quality. No low-quality studies were identified.

**Meta-analysis outcomes**

ESD was performed for a total of 291 dysplastic lesions in 274 patients with IBD. The pooled rates of en-bloc, R0, and curative resections were 92.5% (95% CI, 87.9%–95.4%; \( I^2=0\% \)) (forest plot, Fig. 1), 81.5% (95% CI, 72.5%–88%; \( I^2=43\% \)) (forest plot, Fig. 2), and 48.9% (95% CI, 32.1%–65.9%; \( I^2=87\% \)) (forest plot, Fig. 3), respectively. The local recurrence and metachronous recurrence rates were 3.9% (95% CI, 2%–7.5%; \( I^2=0\% \)) (forest plot, Supplementary Fig. 3) and 10% (95% CI, 5.2%–18.2%; \( I^2=55\% \)) (forest plot, Supplementary Fig. 4), respectively.

The rate of additional surgery following ESD was 13% (95% CI, 8.5%–19.3%; \( I^2=54\% \)) (forest plot, Supplementary Fig. 5). The causes for requiring additional surgery after ESD included presence of superficial or submucosal tumor invasion, lymphatic and vascular involvement, metachronous lesions, invasive adenocarcinoma, and medically refractory disease. One patient with severe submucosal fibrosis received surgery after unsuccessful ESD.

The pooled rates of bleeding and perforation were 7.7% (95% CI, 4.5%–13%; \( I^2=10\% \)) (forest plot, Supplementary Fig. 6) and 5.3% (95% CI, 3.1%–8.9%; \( I^2=0\% \)) (forest plot, Supplementary Fig. 7), respectively. When perforation occurred during ESD, it was treated endoscopically using clip placement and did not require surgery. The pooled rates and \( I^2\% \) values are summarized in Table 3.

**Subgroup and meta-regression analysis**

1) **Subgroup analysis based on IBD type (UC only and UC+CD)**

In nine studies, ESD for colorectal dysplasia was performed in patients with UC only. Three studies have reported on ESD for colorectal dysplasia in both UC and CD. The en-bloc resection rates were 92.2% (95% CI, 86.2%–95.8%) in studies with UC and 93% (95% CI, 84.1%–97.1%) in studies with UC+CD. The R0 resection rates were 81% (95% CI, 70.9%–88.2%) for UC and 83.5% (95% CI, 59.3%–94.6%) for UC+CD. The rest of the subgroup analyses were limited owing to fewer studies on the UC+CD group. The results are summarized in Table 3.

2) **Subgroup analysis based on sample size (<20 or >20) and study geography**

Six studies had a sample size of <20 patients. Equally, six studies had a sample size of >20 patients. Three, six, and three studies were conducted within the US, Asia, and outside the US and Asia (Italy and United Kingdom), respectively. The subgroup analysis based on study sample size and geography was primarily performed for sensitivity analysis to ascertain potential contribution toward the observed heterogeneity. The outcomes were comparable in studies performed in the US, Asia, and other regions. The results are summarized in Supplementary Table 2.

A meta-regression analysis was performed based on lesion location (right or left), morphology (polypoid or nonpolypoid), lesion borders (distinct or indistinct), and surrounding mucosa (remission or active). However, statistical analysis was not feasible due to the limited number of studies.

**Validation of meta-analysis results**

1) **Sensitivity analysis**

To assess whether any study had a dominant effect on the meta-analysis outcomes, we excluded one study at a time and analyzed its effects on the main summary estimate. In this analysis, no single study significantly affected the outcome or heterogeneity.

2) **Heterogeneity**

No heterogeneity was noted for the primary outcomes of en-bloc resection, whereas moderate heterogeneity was observed for R0 resection. Overall, heterogeneity was moderate except for curative resection (87%). This was most likely attributable to the lack of a uniform definition for curative resection among the studies. The subgroup analysis demonstrated sample size (<20 vs. >20) as a significant contributor toward the pooled local recurrence. Since the random-effects model was used, the 95% CIs are illustrated in the respective forest plots.
Table 1. Study and population characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Patients (n)</th>
<th>Sex (M/F)</th>
<th>Median age (y)</th>
<th>UC duration (y)</th>
<th>Lesions (n)</th>
<th>Mean size (mm)</th>
<th>Location (n, R/L)</th>
<th>Morphology (n, P/NP)</th>
<th>Border (n, distinct/indistinct)</th>
<th>Surrounding mucosa (n, R/A)</th>
<th>Submucosal fibrosis (n, present/absent)</th>
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<td>62</td>
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<td>20</td>
<td>7/0/2</td>
<td>11</td>
<td>30</td>
<td>3/8</td>
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<td>7</td>
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</table>

M, male; F, female; UC, ulcerative colitis; E, extensive; L, left-sided; P, proctitis R, right; L, left; P, polypoid; NP, nonpolypoid; R, reactive; A, active; NA, not applicable.
<table>
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<tr>
<th>Study</th>
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<th>en-bloc resection (n)</th>
<th>R0 resection (n)</th>
<th>Curative resection (n)</th>
<th>Bleeding</th>
<th>Perforation</th>
<th>Local recurrence (n)</th>
<th>Metachronous tumors (n)</th>
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<td>SSA/P 1, IND 1, LGD 8, HGD 3, adenocarcinoma 2</td>
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</table>

ESD, endoscopic submucosal dissection; SSA, sessile serrated adenoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IND, indefinite dysplasia; SSA/P, SSA/polyp; NA, not applicable.
**En bloc resection**

<table>
<thead>
<tr>
<th>Group by IBD type</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Event rate and 95% CI</th>
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<tr>
<td></td>
<td></td>
<td>Event rate</td>
<td>Lower limit</td>
</tr>
<tr>
<td>UC</td>
<td>Iacopini, 2015</td>
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<td>Kinoshita, 2019</td>
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<td>Matsu, 2021</td>
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<td>0.678</td>
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<td>UC</td>
<td>Nishio, 2020</td>
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<td>Suzuki, 2017</td>
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<td>0.746</td>
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<td>Yang DH, 2019</td>
<td>0.933</td>
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<td>Poolled</td>
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<tr>
<td>Overall</td>
<td>Prediction interval</td>
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**Fig. 1.** Forest plot for en-bloc resection. IBD, inflammatory bowel disease; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease.

**R0 resection**

<table>
<thead>
<tr>
<th>Group by IBD type</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Event rate and 95% CI</th>
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<td></td>
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<td>Event rate</td>
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<td>Kinoshita, 2019</td>
<td>0.760</td>
<td>0.558</td>
</tr>
<tr>
<td>UC</td>
<td>Matsumoto, 2019</td>
<td>0.667</td>
<td>0.376</td>
</tr>
<tr>
<td>UC</td>
<td>Manta, 2021</td>
<td>0.962</td>
<td>0.861</td>
</tr>
<tr>
<td>UC</td>
<td>Matsu, 2021</td>
<td>0.706</td>
<td>0.458</td>
</tr>
<tr>
<td>UC</td>
<td>Nishio, 2020</td>
<td>0.974</td>
<td>0.839</td>
</tr>
<tr>
<td>UC</td>
<td>Suzuki, 2017</td>
<td>0.719</td>
<td>0.542</td>
</tr>
<tr>
<td>UC</td>
<td>Yang DH, 2019</td>
<td>0.800</td>
<td>0.530</td>
</tr>
<tr>
<td>UC</td>
<td>Poolled</td>
<td>0.810</td>
<td>0.709</td>
</tr>
<tr>
<td>UC</td>
<td>Prediction interval</td>
<td>0.810</td>
<td>0.485</td>
</tr>
<tr>
<td>UC+CD</td>
<td>Lightner, 2021</td>
<td>0.920</td>
<td>0.731</td>
</tr>
<tr>
<td>UC+CD</td>
<td>Ngamruengphong, 2022</td>
<td>0.756</td>
<td>0.610</td>
</tr>
<tr>
<td>UC+CD</td>
<td>Poolled</td>
<td>0.835</td>
<td>0.593</td>
</tr>
<tr>
<td>UC+CD</td>
<td>Prediction interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Poolled</td>
<td>0.815</td>
<td>0.725</td>
</tr>
<tr>
<td>Overall</td>
<td>Prediction interval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Forest plot for R0 resection. IBD, inflammatory bowel disease; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease.
Curative resection

<table>
<thead>
<tr>
<th>Group by IBD type</th>
<th>Study name</th>
<th>Event rate and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC</td>
<td>Iacopini, 2015</td>
<td>0.700 0.536 0.900 7/10</td>
<td>14.05</td>
</tr>
<tr>
<td>UC</td>
<td>Kasuga, 2021</td>
<td>0.818 0.493 0.954 9/11</td>
<td>12.83</td>
</tr>
<tr>
<td>UC</td>
<td>Kinoshita, 2019</td>
<td>0.560 0.366 0.737 14/25</td>
<td>18.00</td>
</tr>
<tr>
<td>UC</td>
<td>Matsumoto, 2019</td>
<td>0.667 0.376 0.869 8/12</td>
<td>15.12</td>
</tr>
<tr>
<td>UC</td>
<td>Manta, 2021</td>
<td>0.962 0.861 0.991 51/53</td>
<td>13.63</td>
</tr>
<tr>
<td>UC</td>
<td>Matsui, 2021</td>
<td>0.706 0.458 0.872 12/17</td>
<td>16.24</td>
</tr>
<tr>
<td>UC</td>
<td>Nishio, 2020</td>
<td>0.974 0.839 0.996 38/39</td>
<td>10.14</td>
</tr>
<tr>
<td>UC</td>
<td>Pooled</td>
<td>0.804 0.631 0.908</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>Prediction interval</td>
<td>0.804 0.206 0.985</td>
<td></td>
</tr>
<tr>
<td>UC+CD</td>
<td>Ngaruangphong, 2022</td>
<td>0.067 0.022 0.187 3/45</td>
<td>100.00</td>
</tr>
<tr>
<td>UC+CD</td>
<td>Pooled</td>
<td>0.067 0.022 0.187</td>
<td></td>
</tr>
<tr>
<td>UC+CD</td>
<td>Prediction interval</td>
<td>0.489 0.321 0.659</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Pooled</td>
<td>0.489 0.017 0.982</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Prediction interval</td>
<td>0.489 0.321 0.659</td>
<td></td>
</tr>
</tbody>
</table>

Overall P<87%
UC=71%
UC+CD=0%

3) Publication bias
No publication bias was noted based on the qualitative assessment of the funnel plot (Supplementary Fig. 8) and quantitatively by Egger's regression analysis (two-tailed p-value = 0.06).

4) Quality of evidence
The GRADE working group approach was used to rate the quality of evidence for results from this meta-analysis. Based on the retrospective nature of included studies and moderate heterogeneity, this meta-analysis would be considered to have low-quality of evidence.

DISCUSSION
In this meta-analysis of twelve studies, ESD demonstrated an excellent pooled en-bloc (92.5%) and R0 (81.5%) resection rate for colorectal dysplasia in patients with IBD. The local recurrence rate was 3.9%, with low pooled rates of adverse events, including bleeding (7.7%) and perforation (5.3%). To the best of our knowledge, with 291 dysplastic lesions in 274 patients with IBD, this study reports the largest pooled data of ESD for colorectal dysplasia in patients with IBD.

The current ASGE guidelines regarding the management of colorectal dysplasia in IBD recommend en-bloc resection by EMR or ESD of endoscopically visible lesions with distinct borders instead of surgery. EMR has been associated with a 27%–63% en-bloc resection rate and a 14% to 50% local recurrence rate. In this study, although 73.1% of dysplastic lesions had submucosal fibrosis, ESD demonstrated excellent en-bloc and R0 resection rates along with low rates of local recurrence, perforation, and bleeding.

ESD in patients with IBD can present technical challenges if the submucosal fibrosis is extensive. This is reflected in our study with a metachronous recurrence rate of 20%. Despite this, we demonstrate that the need for surgery was low at 13%, with a curative resection rate of 48.9%. This may be attributed to not all patients with failed resection receiving surgery. Additionally, the rate of curative resection needs to be interpreted with caution as a certain level of variability was observed in how the individual studies defined ‘curative resection’, which also explains the high heterogeneity (87%). The most consistent definition for ‘curative resection’ was when pathological findings revealed R0 resection without any of the following features: submucosal deep invasion (≥1,000 μm), lymphovascular involvement, or poorly differentiated adenocarcinoma component. The reported pooled rates are encouraging and highlight the importance of frequent endoscopic surveillance following ESD to monitor for local and metachronous recurrence in patients with IBD.
Table 3. Summary of pooled rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled rate (95% confidence interval)/no. of study</th>
<th>% heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>En-bloc resection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>92.5 (87.9–95.4)/12</td>
<td>0</td>
</tr>
<tr>
<td>UC</td>
<td>92.2 (86.2–95.8)/9</td>
<td>7</td>
</tr>
<tr>
<td>UC+CD</td>
<td>93(84.1–97.1)/3</td>
<td>0</td>
</tr>
<tr>
<td>R0 resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>81.5 (72.5–88)/11</td>
<td>43</td>
</tr>
<tr>
<td>UC</td>
<td>81 (70.9–88.2)/9</td>
<td>47</td>
</tr>
<tr>
<td>UC+CD</td>
<td>83.5 (59.3–94.6)/2</td>
<td>61</td>
</tr>
<tr>
<td>Curative resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>48.9 (32.1–65.9)/8</td>
<td>87</td>
</tr>
<tr>
<td>UC</td>
<td>80.4 (63.1–90.8)/7</td>
<td>71</td>
</tr>
<tr>
<td>UC+CD</td>
<td>6.7 (2.2–18.7)/1</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7.7 (4.5–13)/12</td>
<td>10</td>
</tr>
<tr>
<td>UC</td>
<td>7.9 (3.9–15.4)/9</td>
<td>26</td>
</tr>
<tr>
<td>UC+CD</td>
<td>7.5 (3.1–16.7)/3</td>
<td>0</td>
</tr>
<tr>
<td>Perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5.3 (3.1–8.9)/12</td>
<td>0</td>
</tr>
<tr>
<td>UC</td>
<td>5.9 (3.3–10.3)/9</td>
<td>0</td>
</tr>
<tr>
<td>UC+CD</td>
<td>3.5 (1–11.5)/3</td>
<td>0</td>
</tr>
<tr>
<td>Local recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.9 (2–7.5)/12</td>
<td>0</td>
</tr>
<tr>
<td>UC</td>
<td>4.3 (2–9)/9</td>
<td>0</td>
</tr>
<tr>
<td>UC+CD</td>
<td>2.9 (0.7–10.8)/3</td>
<td>0</td>
</tr>
<tr>
<td>Metachronous recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10 (5.2–18.2)/11</td>
<td>55</td>
</tr>
<tr>
<td>UC</td>
<td>10 (5.1–18.6)/9</td>
<td>48</td>
</tr>
<tr>
<td>UC+CD</td>
<td>10.3 (0.8–61.3)/2</td>
<td>71</td>
</tr>
<tr>
<td>Additional surgery after ESD</td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13 (8.5–19.3)/12</td>
<td>54</td>
</tr>
<tr>
<td>UC</td>
<td>12.8 (8.3–19.4)/9</td>
<td>81</td>
</tr>
<tr>
<td>UC+CD</td>
<td>15.7 (2.9–54)/3</td>
<td>16</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>72.7 (53.2–92.2)</td>
<td>92</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Absent (Egger's 2-tailed p=0.06)</td>
<td></td>
</tr>
</tbody>
</table>

UC, ulcerative colitis; CD, Crohn’s disease; ESD, endoscopic submucosal dissection.

EMR is increasingly being performed in the US, whereas ESD remains a complex procedure only performed by experienced endoscopists in select IBD centers. In our analysis, the pooled mean procedure time was 72.7 minutes, which is comparable to the mean procedure time in ESD for sporadic CRC (75–106 minutes). As the current literature demonstrates the increasing feasibility of ESD for complex lesions in IBD, we anticipate increased utilization of this technique with additional focused training.

In our subgroup analyses, we observed that pooled rates from studies with a sample size of >20 patients demonstrated lower rates of local recurrence (2% vs 7.3%). Although no studies that were exclusively performed in patients with CD were identified, we noted that the outcomes were slightly better in study samples that included both CD and UC compared to UC alone. Whether this is directly related to the differences in the underlying pathology of CD vs. UC or to the higher risk of dysplastic lesions in UC with varying grades of active inflammation contributing to indistinct lesion borders remains unknown.

A meta-analysis by Mohapatra et al. summarized the results of 190 colorectal dysplastic lesions undergoing ESD and revealed an en-bloc resection rate of 85.7% in patients with IBD. Similarly, a meta-analysis by Chen et al. demonstrated an en-bloc resection rate of 86% with ESD for non-polypoid dysplasia in patients with IBD. Our study demonstrated a higher en-bloc resection rate (92.5%) than the previous studies which may be attributed to the larger sample size with more recent studies included in our analysis. Recent advances in ESD techniques and emphasis on advanced training may have contributed to these findings.

Our study has several strengths. The literature search was rigorously performed to include studies that used ESD for colorectal dysplasia in IBD. No low-quality studies were identified in this analysis, and no heterogeneity was reported on the primary outcomes of en-bloc and R0 resection. As noted above, although studies reporting outcomes of advanced endoscopic resection techniques for colorectal dysplasia exist, the present study is the
most up-to-date meta-analysis specifically evaluating outcomes of ESD technique for colorectal dysplasia in IBD.

This study had some limitations, most of which are inherent to any meta-analysis of retrospective studies with a potential risk of selection bias. Patient-level granular information regarding the severity of disease, extent of disease, and endoscopic remission status at the time of ESD was not available. Furthermore, information regarding the criteria of lesion selection, degree of dysplasia, timing of bleeding (immediate/delayed), and outcomes of patients who did not receive additional surgery after ESD could not be ascertained from all the studies. Additionally, concomitant high-risk features, such as positive family history, prior personal history of high-risk dysplasia, and primary sclerosing cholangitis, were not reported. Nevertheless, the pooled data from this study adds valuable information to the current literature on this topic.

In conclusion, this meta-analysis demonstrates ESD to be safe and effective for colorectal dysplasia in IBD. ESD demonstrates excellent en-bloc and R0 resection rate, with low rates of local recurrence and adverse events. The reported rates of curative resection warrant further studies with uniform definition to validate our findings.

Supplementary Material

Supplementary Table 1. Study quality assessment using the Newcastle–Ottawa scale.

Supplementary Table 2. Subgroup sensitivity analyses.

Supplementary Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Supplementary Fig. 2. Forest plot for procedure time.

Supplementary Fig. 3. Forest plot for bleeding.

Supplementary Fig. 4. Forest plot for perforation.

Supplementary Fig. 5. Forest plot for local recurrence.

Supplementary Fig. 6. Forest plot for metachronous tumors.

Supplementary Fig. 7. Forest plot for additional surgery after endoscopic submucosal dissection.

Supplementary Fig. 8. Funnel plot for publication bias.

Supplementary Material 1. Literature search strategy.

Supplementary Material 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.


Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.205.

Ethical Statements

Not applicable.

Conflicts of Interest

Mohamed O. Othman is a consultant for Olympus, Boston Scientific, Creo Medical, Lumendi, Abbvie, Nestle, Ambu, and Conmed. Peter V. Draganov is a consultant for Olympus, Fujifilm, Boston Scientific, Microtech, and Medtronic. Gursimran S. Kochhar is on the Advisor board for GIE Medical, Lilly Pharmaceuticals, and Corvetas Research Foundation. Gursimran S. Kochhar is a consultant for Pentax Endoscopy, Boston Scientific Endoscopy and Olympus Endoscopy. Gursimran S. Kochhar is a speaker for Lilly Pharma. The other authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: TFM, BPM, GSK, AUR, MOO, PVD; Data curation: TFM, BPM, VS; Formal analysis: BPM; Investigation: TFM, BPM; Project administration: TFM, BPM; Resources: TFM, BPM; Software: TFM, BPM; Writing–original draft: TFM, BPM; Writing–review & editing: all authors.

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REFERENCES


32. Patel N, Patel K, Ashrafian H, et al. Colorectal endoscopic submu-


Endoscopic resection penetrating the muscularis propria for gastric gastrointestinal stromal tumors: advances and challenges

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Gastric subepithelial tumors grow within the gastric wall; therefore, endoscopic removal requires advanced techniques and experienced hands. Gastrointestinal stromal tumors (GISTs) are the most common gastric subepithelial tumors with malignant potential. Endoscopic ultrasonography is the most accurate noninvasive method for evaluating layers and echo patterns. GIST originates from the muscularis propria layer, which is divided into submucosal, intramuscular, or subserosal types according to endoscopic ultrasonography findings. Conventional endoscopic submucosal dissection (ESD) is a useful technique for removing the submucosal type and is associated with a low risk of adverse events. Endoscopic full-thickness resection (EFTR) may sometimes be required for submucosal-growing GIST. The intramuscular and subserosal patterns indicate that the tumor has an extensive muscularis involvement or penetration beyond the gastric wall. Endoscopic resection is associated with a high possibility of full-thickness resection, which involves peritoneal tumor cell seeding and gastric juice leakage. In addition, the complete resection (R0 resection) rate is relatively low for tumors originating from the muscularis propria compared to those reported in studies on early gastric cancers. GISTs have pseudocapsules to prevent the tumor cell spillage, and microscopic incomplete resection (R1 resection) is not significant for local recurrence in many studies. Recently, the European Society of Gastrointestinal Endoscopy guidelines recommended EFTR as an alternative to laparoscopic wedge resection for gastric GIST <3.5 cm.

An ideal EFTR must have the least peritoneal tumor cell exposure, minimal gastric juice leakage, and a high complete resection rate. Conventional EFTR is based on an ESD technique combined with clip closure; however, it has limitations in viewing the dissecting area and achieving good closure with clipping. Submucosal tunneling endoscopic resection results in good closure after full-thickness resection and is associated with a low risk of gastric juice leakage. Submucosal tunneling endoscopic resection is only possible in the cardia and esophagogastric junction, which is a serious limitation.

The gastric full-thickness resection device is a modified version of the Over-The-Scope Clip, which has the advantages of good closure and low risk of peritonitis. However, it may be useful for tumors <1 cm. Although various full-thickness resection techniques have been developed, they are challenging. Precise muscular dissection must be achieved for en bloc resection without injuring the pseudocapsule. Complete closure is important to avoid tumor cell seeding and peritonitis after full-thickness resection.
resection. Most techniques using clips, snares, and threads have been reported to provide a good dissection view and a low risk of peritoneal tumor cell exposure.\textsuperscript{7,8}

In a study by Kim et al.\textsuperscript{9}, EFTR using a modified technique, termed clip-and-cut EFTR (cc-EFTR), was performed in 32 patients. Most lesions (86.3\%) were in the upper third of the stomach, and 71.9\% of the tumors had subserosal growth patterns. The R0 resection rate was 84.4\%, and two cases of localized peritonitis were treated conservatively. No recurrence was observed 25 months after the treatment. In cc-EFTR, a clip connected to dental floss is attached to the dissected flap edge for tumor mass traction. The clip is fixed at both ends of the dissected area for a good approximation of the penetrated muscularis propria, followed by stepwise clipping immediately after the transmural cut.

EFTR has been used to treat GISTs but has not yet been standardized. Submucosal and muscular dissections were performed using a technique like that used in ESD. Full-thickness resection and closure are the most important steps that must be addressed. The cc-EFTR technique is relatively simple and easy to perform compared to previously reported methods. Complete closure was made in most cases with a high R0 resection rate. I believe that cc-EFTR will be a useful technique for full-thickness resection of fundus and upper body tumors.

Endoscopy is increasingly used to treat gastric GISTs. Small gastric (<3.5 cm) subepithelial tumors with endophytic growth are good indications for endoscopic resection, even those with significant muscularis propria involvement. The treatment of choice for exophytic growing tumors is laparoscopic wedge resection, which has significant normal tissue loss and some limitations for tumors in special locations, such as the esophagogastric junction, cardia, or lesser curvature.\textsuperscript{9} Endoscopic resection minimizes gastric tissue loss and prevents gastroparesis and gastric deformities. cc-EFTR can be a standard technique for fundus or upper body tumors with exophytic growth of less than one-third of the tumor volume. Recently, endoscopic subserosal dissection was introduced to treat tumors with exophytic growth. Endoscopic subserosal dissection is a technique that penetrates the muscularis propria layer and dissects the subserosal layer, which is useful in the esophagogastric junction, cardia, fundus and upper body parts, lesser curvature, and greater curvature.\textsuperscript{10}

Small gastric subepithelial tumors can be safely treated with endoscopic resection (Fig. 1). Studies on EFTR for gastric GISTs have been increasing, and technical advancements have been achieved. Endoscopic resection is expected to become a standard treatment for GIST soon.

**Fig. 1.** Suggested algorithm of endoscopic resection for gastric small (<3.5 cm) subepithelial tumors. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EG, esophagogastric; ESSD, endoscopic subserosal dissection; STER, submucosal tunneling endoscopic resection; EMD, endoscopic muscular dissection; EFTR, endoscopic full-thickness resection; EUS-FNA/B, EUS guided fine-needle aspiration/biopsy.
Conflicts of Interest
The author has no potential conflicts of interest.

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REFERENCES
Cholangiocarcinoma (CCA) incidence is significantly higher in Asian countries (including Korea, China, and Thailand) than in other geographical regions, potentially attributed to parasitic infections, notably those related to *Clonorchis sinensis*. The poor CCA prognosis is mostly due to advanced-stage diagnosis and the limited effectiveness of available medical interventions, including targeted therapy and chemotherapeutics. The gemcitabine plus cisplatin (GP) regimen has been established as the first-line chemotherapy for CCA since the early 2000s. Despite high expectations, the addition of nab-paclitaxel to the GP regimen failed to demonstrate a significant extension in survival in a phase 3 study.1,2 The recent National Comprehensive Cancer Network guidelines have included immune checkpoint inhibitors (e.g., durvalumab or pembrolizumab) to the GP regimen for CCA treatment. However, this approach is reportedly largely ineffective, since survival periods were extended by approximately one month only (D+GP vs. GP, 12.8 vs. 11.5 months; P+GP vs. GP, 12.7 vs. 10.9 months).3,4 According to the location and growth patterns, CCA comprises intrahepatic, perihilar, and extrahepatic subtypes as well as intraductal, ductal, and mass-forming types, respectively. These classifications have been associated with distinct prognoses and genetic variants. Consequently, a better understanding of the unique characteristics of these subtypes, including genetic studies, would be warranted and would enable the pursuit of customized precision medicine therapeutics for individual patients, thereby potentially overcoming therapeutic challenges. Pathogenic variants of intrahepatic CCA include FGFR2, IDH1/2, EPHA2, BAP1, KRAS, SMAD4, ARID1A, GNAS, TP53, BRCA1/2, ERBB2, and PIK3CA. In addition, the genetic variants of PRKACA/B, ELF3, ARID1A/B, KRAS, SMAD4, GNAS, TP53, BRCA1/2, ERBB2, and PIK3CA have been implicated in extrahepatic CCA. Furthermore, gallbladder carcinoma (GBC) is associated with pathogenic EGFR, ERBB2/3, PTEN, ARID2, MLL2/3, TERT, TP53, BRCA1/2, and PIK3CA variants.5 FGFR2 variants have been studied extensively in the context of intrahepatic CCA, and therapies targeting such genetic changes, including pemigatinib and futibatinib, demonstrated promising response rates of 35.5% and 42%, respectively, when used as second-line
CCA diagnosis is predominantly confirmed via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous liver biopsy in advanced stages. The diagnostic technique selection being influenced by the anatomical location of the tumor. The lower sensitivity of the ERCP biopsy led to a growing preference for fine-needle aspiration (FNA) and fine-needle biopsy (FNB), facilitated by endoscopic ultrasound (EUS). A recent meta-analysis revealed ERCP and EUS-FNA sensitivity, specificity, and diagnostic accuracy, in the context of malignant biliary strictures, as 49% and 75%, 96.3% and 100%, and 60.6% and 79%, respectively. Comprehensive genomic profiling (CGP) requires higher tissue quantity than that routinely required for pathological diagnosis. Therefore, percutaneous liver biopsy or surgical biopsy are commonly employed to obtain sufficient CGP material. However, such procedures are more invasive and carry a higher complication risk than EUS-FNA or EUS-FNB. Therefore, the latter procedure could be considered a chosen diagnostic technique if an acceptable diagnostic rate and CGP adequacy could be irrefutably demonstrated. Several studies using CCA tissue for CGP harvested via EUS-FNB described pathogenic variant detection rates of 0% to 30%. However, the tissue quantity adequacy rates remained undocumented in these reports. These studies were predominantly limited by patient selection, with most enrolled patients suffering from intrahepatic CCA or GBC and very few cases representing ductal infiltration and extrahepatic CCA. Notably, a study evaluating EUS-FNA efficacy in pancreatic cancer reported CGP adequacy rates of 72.5%, 53.5%, and 33.3% for 19-G-FNB, 22-G-FNB, and 22-G-FNA, respectively. This result implies that EUS-FNA could lead to positive results with minimal complications compared to traditional laparoscopic biopsy in pancreatic cancer diagnosis. These findings imply that transitioning from percutaneous methods to EUS-FNA could be advantageous for CCA diagnosis, highlighting the potential benefits of this approach in obtaining tissue samples for genetic analysis with minimal complications.

In the current issue of Clinical Endoscopy, the clinical utility of EUS tissue acquisition for CGP in patients with biliary tract cancer, especially those with intrahepatic CCA, is highlighted by including a larger cohort of 94 patients, surpassing the number of participants in previous articles with similar objectives. Factors positively associated with sample adequacy included the use of a larger needle gauge (19-G vs. 22-G, 93.1% vs. 54.5%; p=0.013), FNB needle type choice (FNA vs. FNB, 37.5% vs. 83.7%; p=0.013), primary lesion presence instead of metastasis (p=0.015), target size >30 mm (p<0.001), and performing >3 punctures (p=0.016).

This study describes the genomic analysis of tissue samples obtained via EUS-FNB to evaluate eight critical therapeutic molecular markers as follows: IDH1 variants (involved in metabolic pathways); FGFR2 fusions (keys to cell growth and angiogenesis); neurotrophic receptor tyrosine kinase (NTRK) fusions (important for neural development and function); BRAF V600E variants (keys to the MAPK signaling pathway); receptor tyrosine-protein kinase erbB-2 (ERBB2) amplifications (associated with cell proliferation and survival); rearrangements during transfection (RET) fusions (impacting cell growth and differentiation); microsatellite instability-high status (indicative of a defective DNA mismatch repair system); and tumor mutational burden (TMB, reflecting the number of mutations carried by tumor cells). FGFR2 fusions were detected in 12.9% of intrahepatic CCA, making it the most prevalent variant. IDH1 variants were the second most common genetic cause of intrahepatic CCA (9.7%). While GBC frequently (21.4%) exhibited ERBB2 amplification as the primary alteration, TMB-high status (17.9%) was the second most common variation. Furthermore, the pathogenic variant detection rate in intrahepatic CCA and GBC was approximately 30%, being notably lower than that in extrahepatic CCA (0%). KRAS and TP53 status evaluations in intrahepatic CCA (32.3% vs.32.3%), extrahepatic CCA (35.7% vs.71.4%), and GBC (7.1% vs.53.6%) revealed significant differences with a particularly lower KRAS variant detection rate in GBC compared to that in CCA (7% vs. 33%, p=0.011).

This study was limited by the fact that most of the enrolled patients displayed intrahepatic CCA and GBC. In addition, only four patients underwent targeted assessment of the bile duct using EUS-FNA/B, with adequate tissue collection in 50% of these cases. Consequently, this study might not have fully captured the specificity of ductal infiltration types and extrahepatic CCA within the CCA category. In contrast, this study highlights successful CGP performance in intrahepatic and mass-forming CCA using EUS-FNA/B. Furthermore, large-scale studies assessing CGP feasibility in patients with ductal infiltration types undergoing EUS-FNA/B are crucial for developing diagnostic strategies to combat CCA.
Conflicts of Interest
The authors have no potential conflicts of interest.

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Author Contributions
Conceptualization: SYH; Data curation: JL; Formal analysis: JL; Funding acquisition: SYH; Investigation: JL; Methodology: JL; Project administration: SYH; Resources: JL; Software: JL; Supervision: SYH; Validation: JL; Visualization: JL; Writing—original draft: SYH; Writing—review & editing: all authors.

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REFERENCES
15. Idossa D, Borrero M, Blaes A. ERBB2-low (also known as HER2-low) breast cancer. JAMA Oncol 2023;9:576.
Aerosol protection using modified N95 respirator during upper gastrointestinal endoscopy: a randomized controlled trial

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**Results:**
There was a statistically significant increase in 0.3-μm particle size in the control group compared to modified N95 group (242 x 103 counts/m² vs. 68 x 10³ counts/m², p<0.045). The amount of particle size over 0.3 μm was also higher in the control group.

No correlations between body mass index, choice of anesthesia, smoking, previous COVID-19 or respiratory tract disease, endoscopic duration, and the overall increased particle counts in both groups.

No adverse event was observed in both groups. The device did not cause any inconvenience for endoscopists and patients.

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Background/Aims: The coronavirus disease 2019 pandemic has affected the worldwide practice of upper gastrointestinal endoscopy. Here we designed a modified N95 respirator with a channel for endoscope insertion and evaluated its efficacy in upper gastrointestinal endoscopy.

Methods: Thirty patients scheduled for upper gastrointestinal endoscopy were randomized into the modified N95 (n=15) or control (n=15) group. The mask was placed on the patient after anesthesia administration and particles were counted every minute before (baseline) and during the procedure by a TSI AeroTrak particle counter (9306-04; TSI Inc.) and categorized by size (0.3, 0.5, 1, 3, 5, and 10 µm). Differences in particle counts between time points were recorded.

Results: During the procedure, the modified N95 group displayed significantly smaller overall particle sizes than the control group (median [interquartile range], 231 [54–385] vs. 579 [213–1,379] ×10³/m³; p=0.056). However, the intervention group had a significant decrease in 0.3-µm particles (68 [–25 to 185] vs. 242 [72–588] ×10³/m³; p=0.045). No adverse events occurred in either group. The device did not cause any inconvenience to the endoscopists or patients.

Conclusions: This modified N95 respirator reduced the number of particles, especially 0.3-µm particles, generated during upper gastrointestinal endoscopy.

Keywords: Aerosols; COVID-19; Endoscopy; Gastroscopy; N95 respirators

INTRODUCTION
Since the advent of the coronavirus disease 2019 (COVID-19) pandemic in 2019, upper gastrointestinal endoscopy has been considered an aerosol-generating procedure.1–3 Several studies have demonstrated the presence of the causative sudden acute respiratory syndrome coronavirus-2 virus in body fluids such as in oropharyngeal secretions. The viral infection is known to spread by aerosol particles <5 µm and droplets >5 µm in size.4–6 Endoscopic procedures have been adjusted to prevent human-to-human transmission.7 For treating patients with COVID-19, full personal protective equipment is mandatory for endoscopists and other healthcare personnel.8,9 However, some patients who test negative for COVID-19 before endoscopy may develop viral infection during the incubation period. Therefore, adequate protection of endoscopy personnel is required to prevent viral spread.

Various novel devices were developed to prevent viral dissemination during endoscopic procedures.10–15 An acrylic box was adapted for endotracheal intubation in COVID-19 patients to decrease the spillage of aerosols and droplets.16 The N95 respirator is a well-known and widely available mask that can filter at least 95% of 0.3-µm particles. Although COVID-19 viral particles are 0.125 µm in diameter, they are mostly adherent to body fluids. Since the N95 respirator can filter aerosols and droplets, thereby preventing viral transmission,17 here we modified the mask to enable endoscopic insertion and measured its efficacy for particle release during upper gastrointestinal endoscopy. We then assessed patient safety and endoscopist feedback.

METHODS

Study design
This study was conducted at the Siriraj Gastrointestinal Endoscopy Center (World Gastroenterology Organization-accredited training center), Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.

Design of modified N95 respirator
A standard N95 respirator (3M Aura 1870+ model; 3M Health Care) was modified to create a channel for endoscopic insertion. In proportion to the 9.9-mm outer diameter of the gastroscope (GIF-HQ190; Olympus), two intersecting 10.4-mm linear puncture holes were created to fit the diameter of the scope to minimize aerosol spread during the procedure. A representative illustration of the modified N95 respirator is provided in Figure 1.

Fig. 1. Illustration of a modified N95 respirator. A standard N95 respirator (3M Aura 1870+ model) was modified as shown. In proportion to the 9.9-mm outer diameter of the gastroscope (GIF-HQ190; Olympus), two intersecting 10.4-mm linear holes were created and fitted to the diameter of the scope. Illustrated by the author.
Participants
All patients aged ≤18 years with undetectable COVID-19 on a nasopharyngeal swab tested by reverse transcriptase polymerase chain reaction within 48 hours of diagnostic upper gastrointestinal endoscopy were enrolled. Patients who required orotracheal intubation, required a transnasal endoscopy route, or had a previous history of upper gastrointestinal surgeries and unrelated procedures were excluded. All eligible patients were monitored during the procedure by an anesthesiologist.

Randomization and procedure
The participants were randomly assigned in a 1:1 ratio to the modified N95 or control group (no mask) using a computer-generated randomization program. Group allocation was performed by a nurse not involved in the procedure using sealed opaque envelopes. After allocation, each patient was transferred to the endoscopic unit and the endoscopic room was sealed to avoid unnecessary traffic that could interfere with particle counts during the procedure. Due to the nature of the intervention, the endoscopists and patients could not be blinded. All procedures were performed in one of two endoscopic rooms: A, room volume of 90 m$^3$ with an air flow change of 25 times/h, and B, room volume of 135 m$^3$ with an air flow change of 15 times/h. The endoscopists and other involved personnel wore surgical masks, gowns, disposable latex gloves, and closed-toe shoes or shoe covers throughout the procedure. All patients were placed in the left lateral decubitus position using supplemental oxygen via a nasal cannula. Anesthesia was chosen based on the anesthesiologist and patient's joint approval. For topical anesthesia before endoscopy, five puffs of 10% lidocaine were sprayed into the patient's mouth twice and retained for 10 seconds each time. A negative gag reflex was confirmed before the endoscopy commenced. For intravenous sedation, 25 to 75 µg/kg/min of propofol and 1 µg/kg of fentanyl were injected intravenously to achieve mild to moderate sedation as per the definition given in the American Society of Anesthesiologists guideline. After adequate anesthesia and oxygenation were ensured, a modified N95 respirator was placed over the patient's nose and mouth in the modified N95 group and an endoscope inserted through the channel. Endoscopic examinations were performed in both groups.

Outcome measurements
A TSI AeroTrak (9306-04) handheld particle counter (TSI Inc.) was used to determine the total number of particles (Fig. 2).

The counter has an acquisition flow rate of 2.83 L/min. Recorded particle sizes were 0.3, 0.5, 1, 3, 5, and 10 µm. The particle counter was placed 1 m away from the patient. The setup of the endoscopic unit is shown in Figure 3. Baseline particle counts were measured in the empty endoscopic room with closed doors for at least 15 minutes in the early morning before the first case of endoscopy that day. During each endoscopic examination, particle counts were measured and recorded every minute from the time of scope intubation to complete scope withdrawal. The primary outcome was the intergroup difference in particle counts during the procedures. The secondary outcomes were factors associated with increased particle counts and adverse events in patients wearing the modified N95 respirator. Feedback from patients and endoscopists was collected after every procedure. Patient demographic data, anesthetic techniques, and details of the upper gastrointestinal endoscopy were recorded.

Statistical analysis
Statistical analysis was performed using SPSS software ver. 18.0 (SPSS Inc.). Continuous variables are expressed as number (%) and mean±standard deviation for normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables. The increased intergroup particle counts were compared using the Mann-Whitney U-test. Factors associated with changes in particle counts during the procedure were analyzed using bivariate correlations. Values of $p<0.05$ were considered statistically significant.

Fig. 2. TSI AeroTrak (9306-04) handheld particle counter (TSI Inc.).
Ethical statements
This single-center randomized controlled study was approved by the Siriraj Institutional Review Board (approval number: Si-017/2022) and registered in the Thai Clinical Trials Registry (TCTR20220121006). Written informed consent was obtained from all participants.

RESULTS
Demographic data
The demographic data and endoscopic details of the N95 and control groups were comparable, including the nature of the disease and procedure time (Table 1). The baseline total particle counts of all particle sizes were also comparable between groups (358; IQR, 276–689 vs. 399; IQR, 288–753×10^3/m^3; p=0.279).

Increased particle counts during endoscopic procedure
A statistically significant increase in 0.3-μm particle size was observed in the control group (242 vs. 68×10^3 counts/m^3; p=0.045). The concentration of 0.3-μm particles was higher, but not statistically significant, in the control group. The control group had greater than two times the overall particles of the modified N95 group (Table 2).

Factors affecting increased particle counts
Our study found no correlation between the following factors: body mass index, choice of anesthesia, smoking, previous history of COVID-19 infection or respiratory tract disease, endoscopic duration, and overall increased particle count in either group (Table 3).

Adverse events
No complications were observed during or after the endoscopic examination in this study. Specifically, respiratory compromise or secretion obstruction were not observed in the modified N95 group during endoscope insertion. In addition, the endoscopists reported an absence of difficulty with endoscope insertion in the modified N95 group. All patients underwent one successful endoscope insertion attempt through the channel created in the modified N95 respirator.

DISCUSSION
Our study assessed the advantages and safety of using a modified N95 respirator for controlling aerosol dissemination in patients that undergo upper gastrointestinal endoscopy. The study demonstrated that our modified N95 respirator reduced

**Fig. 3.** Endoscopic unit setup. The TSI AeroTrak (9306-04; TSI Inc.) handheld particle counter was placed 1 m apart from patient at the same side as the endoscopist, without any blockages, and the endoscope was inserted through the modified N95 respirator. Illustrated by the author.
overall particle spillage by approximately 50% and significantly decreased 0.3-μm particle spillage by 72% versus patients who were unmasked during the endoscopic examination. This suggests that the transmission of COVID-19 viral particles that adhere to aerosols from body fluids can be prevented. Additionally, the respirator did not interfere with endoscopic examination or increase patient complications.

In the recent years of the COVID-19 pandemic, several innovations were proposed for aerosol and droplet prevention. A transparent acrylic box placed over the patient's head effectively reduced the spillage of droplets but interfered with the work of endoscopists. In addition, dental suction reduces the number of particles of all sizes that were detected during upper gastrointestinal endoscopy. Topical anesthetic throat spray and coughing were strongly associated with maximal particle generation throughout upper gastrointestinal endoscopic procedures. In our study, we did not apply any suction devices, as this was not feasible in patients with masks. However, reflex coughing is blunted by intravenous sedation, as seen in patients of our study. It would be interesting to examine the beneficial effects of our respirator in

| Table 1. Patients’ demographic data and endoscopic details |
|---------------------------------|-----------------|-----------------|-----------------|
| **Variable**                      | **Modified N95 (n=15)** | **No mask (n=15)** | **p-value**     |
| Age (yr)                          | 63.9±12.6        | 60.4±16.6        | 0.697           |
| Body mass index (kg/m²)           | 23.9 (22.9–26.3) | 24.9 (23.5–26.6) | 0.414           |
| Female                            | 6 (40.0)         | 10 (66.7)        | 0.272           |
| **Anesthesia**                    |                  |                  | 0.056           |
| Topical                           | 0 (0)            | 4 (26.7)         |                 |
| Total intravenous anesthesia      | 5 (33.3)         | 6 (40.0)         |                 |
| Both                              | 10 (66.7)        | 5 (33.3)         |                 |
| Smoking                           | 0 (0)            | 3 (20.0)         | 0.224           |
| Previous coronavirus disease 2019 infection | 0 (0) | 2 (13.3) | 0.483 |
| History of lung cancer or tuberculosis | 2 (13.3) | 2 (13.3) | >0.999 |
| Endoscopist                       |                  |                  | 0.682           |
| Staff                             | 3 (20.0)         | 5 (33.3)         |                 |
| Resident/fellow                   | 12 (80.0)        | 10 (66.7)        |                 |
| Endoscopic room                   |                  |                  | 0.245           |
| A                                 | 12 (80.0)        | 8 (53.3)         |                 |
| B                                 | 3 (20.0)         | 7 (46.7)         |                 |
| Endoscopic diagnosis: benign⁶⁰    | 15 (100.0)       | 12 (80.0)        | 0.224           |
| Procedure time (min)              | 14 (10–20)       | 15 (11–22)       | 0.165           |
| Add-on procedures⁶¹               | 14 (93.3)        | 13 (86.7)        | >0.999          |

Values are presented as mean±standard deviation, median (interquartile range), or number (%).

⁶⁰A common diagnosis was benign disease: gastritis in 13 patients (43%), gastric ulcers in 3 (10%), intestinal metaplasia in 3 (10%), subepithelial lesions in 3 (10%), gastric polyps in 2 (7%), reflux esophagitis in 1 (3%), and normal in 2 (7%).

⁶¹Add-on procedures included a rapid urease test in 11 patients (37%), tissue biopsy in 3 (10%), and both in 13 (43%). Pathology reports of tissue biopsy included six of gastritis, six of gastric intestinal metaplasia, one of adenomatous polyp of the duodenal bulb, one of diffuse large B-cell lymphoma of the stomach, and one of squamous cell carcinoma of the upper esophagus.

| Table 2. Increased particle count by study group |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| **Overall particle (×10³/m³)**                | **Modified N95  (n=15)** | **No mask (n=15)** | **p-value**     |
| **Particle size (×10³/m³)**                    |                  |                  |                 |
| 0.3 μm                                         | 231 (54–385)     | 579 (213–1,379)  | 0.056           |
| 0.5 μm                                         | 68 (25 to 185)   | 242 (72–588)     | 0.045           |
| 1 μm                                           | 85 (57–111)      | 213 (78–440)     | 0.067           |
| 3 μm                                           | 64 (37–84)       | 87 (47–408)      | 0.250           |
| 5 μm                                           | 23 (12–32)       | 31 (15–71)       | 0.325           |
| 10 μm                                          | 9 (5–14)         | 10 (3–26)        | 0.838           |
| Overall particle (×10³/m³)                     | 231 (54–385)     | 579 (213–1,379)  | 0.056           |

Values are presented as median (interquartile range).

| Table 3. Factors affecting increased particle count in both groups |
|-------------------------------------------------------------------|-----------------|-----------------|-----------------|
| **Factors**                                                      | **r**           | **p-value**     |
| Body mass index                                                 | 0.188           | 0.320           |
| Choice of anesthesia                                             | 0.155           | 0.412           |
| Smoking                                                         | 0.160           | 0.397           |
| Previous coronavirus disease 2019 infection                     | 0.232           | 0.218           |
| Previous respiratory tract disease                              | 0.272           | 0.146           |
| Endoscopic time                                                  | 0.087           | 0.647           |
| Add-on procedure                                                | −0.289          | 0.122           |
patients undergoing upper gastrointestinal endoscopy without sedation.

Owing to the insignificant intergroup difference in counts of particles >0.3 µm, it is possible that the movement and activities of endoscopists and other healthcare personnel in the procedure room could have generated additional particle counts. The additional procedure, rapid urease test or biopsy, requires an additional instrument that is normally kept in a sealed package to avoid diffusion of dust into the air due to its unsealing. Moreover, larger particles can attach to droplets trapped within the mask or gravitate toward the ground before reaching the particle counter. In this study, the particle counter was kept 1 m apart from the patient’s mouth as the distance between the patient’s mouth and the endoscopist’s nose was estimated to be approximately 1 m. Further, a shorter distance could have interfered with the endoscopic procedure.

The strength of this randomized study was the presence of a controlled environment (only two endoscopic rooms with limited traffic were used). Both staff and trainee endoscopists reported no difficulty during endoscopy in patients wearing masks, indicating that a modified N95 respirator could be effectively applied in daily practice. The original N95 respirator is widely available and the N95 respirator modification technique is simple, replicable at any hospital. The application of this modified N95 respirator is protective and practical for patients who may carry the risk of COVID-19 infection and present during their incubation period.

This single-center randomized study has some limitations. First, it included only uncomplicated upper gastrointestinal endoscopies. Therefore, the beneficial effect of respirators on particle reduction in advanced endoscopic interventions such as endoscopic retrograde cholangiopancreatography or endoscopic submucosal dissection should be established. Prolonged endoscopic duration, when multiple additional instruments are inserted through the working channel of the scope, may affect the capability of the mask. Second, the particle counter used to detect particle at 1 m in this study was limited to the detection of 0.3-µm particles. Different particle counters at variable distances may yield differing results. Finally, we used particle size as a surrogate marker for possible airborne viral spread. Whether particle reduction decreases the rate of airborne infection needs to be examined.

In conclusion, this study demonstrated that a modified N95 respirator could reduce the counts of the smallest (i.e., 0.3-µm) particles and decrease the counts of larger particles. Therefore, we conclude that the modified N95 respirator can be safely applied in patients requiring upper gastrointestinal endoscopy, without increasing procedural difficulty for the endoscopist.

Conflicts of Interest
The authors have no potential conflicts of interest.

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Author Contributions
Conceptualization: CN, TA; Data curation: CN, TA, TT; Formal analysis: CN, TA; Investigation: CN, TA, AM, TS; Methodology: CN, TA, VC; Project administration: CN, TA, JS, TP, TT; Resources: CN; Supervision: TA, VC, AM, VL; Validation: CN, TA, VL; Visualization: JS, AT, CP, TP, VT, NS; Writing–original draft: CN; Writing–review & editing: all authors.

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REFERENCES
2. Klompas M, Baker M, Rhee C. What is an aerosol-generating proce-
Clinical outcomes of nonvariceal upper gastrointestinal bleeding in nonagenarians and octogenarians: a comparative nationwide analysis

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Clinical outcomes of nonvariceal upper gastrointestinal bleeding in nonagenarians and octogenarians: a comparative nationwide analysis

Number of Patients≥80-Years-Old Admitted with NVUGIB

- Data source: National Inpatient Sample (NIS) database 2016–2020
- Study design: Retrospective
- Sample size: 279,022 hospitalizations

Nonagenarians admitted with NVUGIB are at a higher mortality risk than octogenarians. While EGD is used to a significant extent in managing NVUGIB among nonagenarians, its utilization is comparatively lower when compared to octogenarians. Gastroenterologists should be prepared to encounter a rising number of NVUGIB in this rapidly-growing population.

In-hospital morality

<table>
<thead>
<tr>
<th>Group</th>
<th>In-hospital Mortality</th>
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<tbody>
<tr>
<td>Octogenarian</td>
<td>3%</td>
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<tr>
<td>Nonagenarian</td>
<td>4%</td>
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</table>

OR, 1.5; 95% CI, 1.3–1.7 in the multivariate regression analysis

Total cost of admission

<table>
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<tr>
<th>Group</th>
<th>Total Cost of Admission</th>
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</thead>
<tbody>
<tr>
<td>Octogenarian</td>
<td>$18,658</td>
</tr>
<tr>
<td>Nonagenarian</td>
<td>$16,812</td>
</tr>
</tbody>
</table>

OR, 0.86; 95% CI, 0.83–0.89 in the multivariate regression analysis

EGD utilization

<table>
<thead>
<tr>
<th>Group</th>
<th>EGD Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octogenarian</td>
<td>48%</td>
</tr>
<tr>
<td>Nonagenarian</td>
<td>36%</td>
</tr>
</tbody>
</table>

Nonagenarians admitted with NVUGIB are at a higher mortality risk than octogenarians. While EGD is used to a significant extent in managing NVUGIB among nonagenarians, its utilization is comparatively lower when compared to octogenarians. Gastroenterologists should be prepared to encounter a rising number of NVUGIB in this rapidly-growing population.

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Background/Aims: Nonagenarians will purportedly account for 10% of the United States population by 2050. However, no studies have assessed the outcomes of nonvariceal upper gastrointestinal bleeding (NVUGIB) in this age group.

Methods: The National Inpatient Sample database between 2016 and 2020 was used to compare the clinical outcomes of NVUGIB in nonagenarians and octogenarians and evaluate predictors of mortality and the use of esophagogastroduodenoscopy (EGD).

Results: Nonagenarians had higher in-hospital mortality than that of octogenarians (4% vs. 3%, p<0.001). EGD utilization (30% vs. 48%, p<0.001) and blood transfusion (27% vs. 40%, p<0.001) was significantly lower in nonagenarians. Multivariate logistic regression analysis revealed that nonagenarians with NVUGIB had higher odds of mortality (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.3–1.7) and lower odds of EGD utilization (OR, 0.86; 95% CI, 0.83–0.89) than those of octogenarians.

Conclusions: Nonagenarians admitted with NVUGIB have a higher mortality risk than that of octogenarians. EGD is used significantly in managing NVUGIB among nonagenarians; however, its utilization is comparatively lower than in octogenarians. More studies are needed to assess predictors of poor outcomes and the indications of EGD in this growing population.

Keywords: Esophagogastroduodenoscopy; Gastrointestinal hemorrhage; Nonagenarians; Octogenarians

INTRODUCTION

Nonvariceal upper gastrointestinal (GI) bleeding (NVUGIB), defined as bleeding not secondary to ruptured esophageal or gastric varices proximal to the ligament of Trietz, is a common cause of hospital admission with an incidence of approximately 80 to 100 cases per 100,000 adults per year and an estimated mortality rate of 2% to 15%. Age is an important predictor of NVUGIB’s severity, as the mortality rate of NVUGIB among patients aged <60 years is approximately zero.

Recent studies have shown that the prevalence of NVUGIB is more common among elderly patients aged >65 years. As our elderly population grows rapidly, more hospitalizations from upper GI bleeding (UGIB) can be reasonably expected. However, despite projections that nonagenarians will comprise 10% of the United States (US) population by 2050, predictors of outcomes and complications among nonagenarians suffering from NVUGIB have not been studied. This study primarily aimed to analyze clinical outcomes and predictors of disease severity and mortality in nonagenarians compared to those in octogenarians admitted to the hospital for NVUGIB.

METHODS

Study design
We conducted a retrospective cross-sectional study utilizing pooled data from the US National Inpatient Sample (NIS) between 2016 and 2020. Our study included patients aged ≥80 years admitted to the hospital with a principal diagnosis of NVUGIB. The Agency for Healthcare Research and Quality maintains the NIS database as a part of the Healthcare Cost and Utilization Project (HCUP). This database is the largest all-payer database obtained from acute-care hospitals across the US. The database contains approximately 40 discharge diagnoses and 25 procedures for every patient based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

Study population
Patients aged ≥80 years with a primary diagnosis indicating active bleeding from an upper GI source were included in our study cohort. If the primary diagnosis did not specify the source of the upper GI bleeding, a possible source of the UGIB had to be associated with a secondary diagnosis. This methodology has been validated in previous studies [1]. The ICD-10 codes used to generate the variables are included in Supplementary Table 1. Patients aged <80 years and elective admissions were excluded from our study. Patients were categorized into those aged ≥90 years (“nonagenarians”) or 80 to 89 years (“octogenarians”).

Study variables and clinical outcomes
Variables, including age, sex, race, insurance status, mortality, and length of stay, were provided by the NIS database. Variables that provided hospital-level information, such as hospital size, location, and teaching status, were also included in the database. The comorbidity variables were generated from ICD-10 codes using Exlixhauser’s Comorbidity Software Refined for ICD-10-CM ver. 2021.1, a software developed by the HCUP. The primary outcome was in-hospital mortality. The secondary outcomes included mean length of stay and total cost of hospitalization. The two study groups were compared in terms of the
proportion of patients who had undergone esophagogastroduodenoscopy (EGD), mechanical ventilation, or received blood transfusion. Subgroup analysis compared the outcomes of nonagenarians who had undergone EGD with those who had not. Moreover, multivariate logistic regression analyses were performed for predictors of mortality and EGD utilization.

Statistical analysis
STATA ver. 15 (StataCorp.) was used to perform statistical analysis. The data analysis results were weighted, given the sampling design of the NIS database. Linear variables were compared between the two groups using the Student t-test. Chi-square tests were used to compare categorical variables. Univariate regression analysis was used to calculate the unadjusted odds ratio (OR) for the primary outcomes. Variables with \( p < 0.2 \) in the univariate analysis were used to build a multivariate logistic analysis model to adjust for potential confounders. Statistical significance was set at \( p < 0.05 \).

Ethical statements
According to Health Insurance Portability and Accountability Act regulations, the study was exempt from Institutional Review Board approval, given that the study source is a limited, anonymous dataset.

RESULTS
The number of patients aged \( \geq 80 \) years admitted with NVUGIB between 2016 and 2020 was 279,022, with 78,462 and 200,560 patients in the nonagenarian and octogenarian groups, respectively. The mean age of patients in the octogenarian group was 84 years. The mean age of those in the nonagenarian group was not measured, as all patients aged \( \geq 90 \) years in the NIS database were 90 years old. Compared with the octogenarians, the nonagenarians were more likely to be white, female, and to have a Charlson’s comorbidity index (CCI) of \( \geq 3 \) (Table 1). CCI is a morbidity score extracted from the NIS database’s ICD-10-CM codes, and it calculates mortality risk. The nonagenarians were less likely to be admitted to a large, urban, or teaching hospital. The inpatient mortality was higher in nonagenarians (4% vs. 3%, \( p < 0.001 \)). Nonagenarians had 50% higher odds of mortality than that of octogenarians in the multivariate logistic regression analysis performed to adjust for confounders (OR, 1.5; 95% confidence interval [CI], 1.3–1.7; \( p < 0.001 \)). The cost of hospitalization was lower in nonagenarians (16,812 US dollars [USD] vs. 18,658 USD), and there was a statistically significant slight increase in the mean length of stay compared with that of octogenarians. Nonagenarians were less likely to undergo EGD (30% vs. 48%, \( p < 0.001 \)), mechanical ventilation (2% vs. 4%, \( p < 0.0001 \)), or receive a blood transfusion (27% vs. 40%, \( p < 0.0001 \)) than octogenarians were (Table 2). A higher proportion of nonagenarians had palliative care consults than octogenarians did (5% vs. 4%, \( p < 0.0001 \)).

Predictors of EGD utilization were measured using multivariate logistic regression analysis. Nonagenarians had lower odds of undergoing EGD after adjusting for multiple patient and hospital factors than octogenarians had (OR, 0.86; 95% CI, 0.83–0.89). The analysis also showed that men and white patients were more likely to undergo EGD (Fig. 1).

A subgroup analysis to compare nonagenarians who had undergone EGD with those who had been managed without EGD revealed a lower percentage of patients with CCI \( \geq 3 \) in the EGD group. The EGD group had a lower percentage of patients with dementia but a higher percentage of patients on long-term aspirin or anticoagulation. The EGD group had a higher rate of acute renal failure, acute respiratory failure, mechanical ventilation, and blood transfusion (Table 3). The two groups’ mortality rate was the same (4% vs. 4%, \( p = 0.48 \)).

Multivariate logistic regression analysis was performed to assess the clinical factors impacting mortality in elderly patients undergoing EGD. It revealed that hypertension and long-term use of aspirin and anticoagulants were associated with improved mortality (Fig. 2). Conversely, higher mortality was associated with cardiovascular diseases, liver disease, cancer, and other factors (Fig. 2).

DISCUSSION
Nonagenarians are expected to account for 10% of the US population by the year 2050, and the proportion of elderly adults suffering from acute UGIB continues to increase. Ultimately, an increase in age often comes with greater comorbidities, some of which require patients to adhere to life-long antiplatelet and anticoagulant medication, placing them at a higher risk of GI bleeding. Fortunately, endoscopic intervention for acute UGIB is well-tolerated and effective in most patients, and the severity of acute UGIB between octogenarians and younger patients is similar. However, until now, no studies have assessed the outcomes of NVUGIB in nonagenarians. In this study, we analyzed the clinical outcomes of nonagenarians compared with
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Octogenarians (%)</th>
<th>Nonagenarians (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td>Long-term use of anticoagulants</td>
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<tr>
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<tr>
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<td></td>
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<tr>
<td>Medium</td>
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<td>30</td>
<td></td>
</tr>
<tr>
<td>Large</td>
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<td>39</td>
<td></td>
</tr>
<tr>
<td>Hospital location</td>
<td></td>
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<td>Urban</td>
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<td>83</td>
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</tr>
<tr>
<td>Teaching</td>
<td>67</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug.
octogenarians admitted to the hospital for NVUGIB. We also analyzed demographic and clinical factors to understand better disease severity and mortality predictors in this age group.

To our knowledge, our study is the first to show that nonagenarians are at higher risk of mortality from UGIB than octogenarians are. This age group has a higher risk of mortality after adjustment for confounders. This novel finding is fascinating, given that in similar studies evaluating the safety and efficacy of endoscopic intervention for acute UGIB secondary to peptic ulcer disease, no differences in mortality between octogenarians and younger patients were found. 15,16 The mortality rate observed in our study was lower as we only assessed the same-admission mortality. In addition, the mortality of NVUGIB has been down-trending over the last two decades. 1 We also observed that nonagenarians underwent EGD and mechanical ventilation at much lower rates and received fewer blood transfusions than octogenarians did. Given that higher rates of palliative care consults were observed within the nonagenarian group compared with those in octogenarians and that nonagenarians tended to have higher CCIs, it is reasonable to assume that invasive interventions were not as frequently pursued due to differences in goals of care associated with advanced age. This can help explain the higher mortality observed in the nonagenarian group.

We conducted a subgroup analysis to compare nonagenarians with NVUGIB who underwent EGD with those who did not. The analysis of baseline characteristics revealed that the EGD group had a lower burden of comorbidities and lower prevalence of dementia (Table 3), suggesting that these patients might have been selected based on better functional status compared with those of patients who had not undergone EGD. In addition, a higher percentage of patients in the EGD group were admitted to teaching and large hospitals, likely due to the higher complexity and severity of admissions in these settings. The EGD group exhibited higher rates of mechanical ventilation and blood transfusion, which can be attributed to the selection of sicker patients for the procedure. One possible explanation for the higher severity of NVUGIB in the EGD group is the higher use of aspirin or anticoagulation (Table 3).

Nevertheless, the mortality rate was similar between the two groups, supporting the safety of EGD in nonagenarians. The factors that could have led to similar mortality between both groups despite the differences in the association of aspirin and anticoagulation use, which was more prevalent in the EGD group, with lower mortality, and the association of dementia, which was more prevalent in the non-EGD group, with higher mortality in patients with NVUGIB (Fig. 2). Moreover, the

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**Table 2. Clinical outcomes of octogenarians and nonagenarians with nonvariceal upper gastrointestinal bleeding**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Octogenarians (%)</th>
<th>Nonagenarians (%)</th>
<th>p-value</th>
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</thead>
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<tr>
<td>Died during hospitalization</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Length of stay (d)</td>
<td>4.8</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cost of hospitalization (USD)</td>
<td>18,658</td>
<td>16,812</td>
<td>&lt;0.001</td>
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<tr>
<td>Acute kidney failure</td>
<td>29</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EGD</td>
<td>48</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>40</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palliative care consults</td>
<td>4</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

USD, United States dollar; EGD, esophagogastroduodenoscopy.

---

**Fig. 1.** Predictors of esophagogastroduodenoscopy utilization in patients ≥80 years with nonvariceal upper gastrointestinal bleeding.
Table 3. Baseline demographic characteristics and hospital outcomes of the two cohorts of nonagenarians with NVUGIB (non-EGD vs. EGD cohort)

<table>
<thead>
<tr>
<th>Nonagenarians</th>
<th>Non-EGD cohort (%)</th>
<th>EGD cohort (%)</th>
<th>p-value</th>
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<tr>
<td>Asian or Pacific Islander</td>
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<tr>
<td>Indicator of sex</td>
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<td>41</td>
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<tr>
<td>Female</td>
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<td>59</td>
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<tr>
<td>Dementia</td>
<td>33</td>
<td>26</td>
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<td>Long-term use of aspirin</td>
<td>15</td>
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<tr>
<td>Long-term use of anticoagulation</td>
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<tr>
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</tr>
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<td>Blood transfusion</td>
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<td>44</td>
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NVUGIB, nonvariceal upper gastrointestinal bleeding; EGD, esophagogastroduodenoscopy; NSAID, nonsteroidal anti-inflammatory drug.

more aggressive management of the sicker patients in the EGD group could have contributed to comparable outcomes. Notably, patients who underwent inpatient EGD might have been affected by coding bias, as their admission to the intensive care unit could have resulted in a higher likelihood of coding for acute organ failure. The large sample size and depth of information collected on our patients’ cohort is a strength of this study. However, one of the study’s limitations was our inability to review electronic medical records to better understand patient-tailored medical decision-making during hospital admission. Moreover, despite identifying various factors through our multivariate analysis that influence mortality in octogenarians and nonagenarians undergoing EGD (Fig. 2), it is challenging to determine the specific indications for EGD in this population based on our retrospective analysis.

In conclusion, managing NVUGIB in elderly patients is com-
Fig. 2. Predictors of mortality in patients ≥80 years with nonvariceal upper gastrointestinal bleeding who had undergone esophagogastro-duodenoscopy.

plex, as older patients carry significantly more morbidities and may require medications that predispose them to NVUGIB. Our study revealed that nonagenarians were at a higher risk of NVUGIB mortality than octogenarians. Moreover, while EGDs were used significantly in managing NVUGIB among nonagenarians, their utilization was comparatively lower than in octogenarians. Moreover, we highlighted different clinical factors that impacted mortality in elderly patients undergoing EGDs. More studies are needed to assess predictors of poor outcomes and indications for EGD among nonagenarians; however, gastroenterologists should be prepared to encounter a rising number of NVUGIB necessitating endoscopic treatment in this rapidly-growing population.

**Supplementary Material**

**Supplementary Table 1.** International Classification of Diseases, Tenth Revision (ICD-10) diagnostic and procedural codes utilized in the study.

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.130.

**Conflicts of Interest**

Michel Kahaleh, MD received grant support from Boston Scientific, Fujinon, Apollo Endosurgery, Cook Endoscopy, Olympus, and MI Tech. He is a consultant for Boston Scientific, ABBvie. None of these funds were related to this study. The other authors have no potential conflicts of interest.

**Funding**

None.

**Author Contributions**

Conceptualization: KE, MK; Methodology: KE, JL, EE, FJ, SN; Supervision: MK, SH; Writing—original draft: JL, KE, EE; Writing—review & editing: KE, JL, FJ, SN, SH, MK.

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**REFERENCES**

Endoscopic resection of gastric gastrointestinal stromal tumor using clip-and-cut endoscopic full-thickness resection: a single-center, retrospective cohort in Korea

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Endoscopic resection of gastric gastrointestinal stromal tumor using clip-and-cut endoscopic full-thickness resection: a single-center, retrospective cohort in Korea

- Endoscopic resection is a safe and effective therapeutic option for the removal of gastric GIST.
- The cc-EFTR method showed a high R0 resection rate, even in areas where ESD cannot be easily performed.
Background/Aims: To overcome the technical limitations of classic endoscopic resection for gastric gastrointestinal stromal tumors (GISTs), various methods have been developed. In this study, we examined the role and feasibility of clip-and-cut procedures (clip-and-cut endoscopic full-thickness resection [cc-EFTR]) for gastric GISTs.

Methods: Medical records of 83 patients diagnosed with GISTs after endoscopic resection between 2005 and 2021 were retrospectively reviewed. Moreover, clinical characteristics and outcomes were analyzed.

Results: Endoscopic submucosal dissection (ESD) and cc-EFTR were performed in 51 and 32 patients, respectively. The GISTs were detected in the upper third of the stomach for ESD (52.9%) and cc-EFTR (90.6%). Within the cc-EFTR group, a majority of GISTs were located in the deep muscularis propria or serosal layer, accounting for 96.9%, as opposed to those in the ESD group (45.1%). The R0 resection rates were 51.0% and 84.4% in the ESD and cc-EFTR groups, respectively. Seven (8.4%) patients required surgical treatment (six patients underwent ESD and one underwent cc-EFTR,) due to residual tumor (n=5) and post-procedure adverse events (n=2). Patients undergoing R0 or R1 resection did not experience recurrence during a median 14-month follow-up period, except for one patient in the ESD group.

Conclusions: cc-EFTR displayed a high R0 resection rate; therefore, it is a safe and effective therapeutic option for small gastric GISTs.

Keywords: Endoscopic full-thickness resection; Endoscopic mucosal resection; Endoscopy; Esophagogastroduodenoscopy; Gastrointestinal stromal tumors

INTRODUCTION

Current clinical guidelines recommend periodic endoscopic surveillance for subepithelial tumors (SETs) <20 mm due to their benign features, while surgical intervention is preferred for large SET lesions. However, certain small SETs have malignant potential, especially gastrointestinal stromal tumors (GISTs). Approximately 3.7% of benign-looking GISTs <20 mm in size have a high mitotic index and rapidly increase in size. Therefore, for small SETs, endoscopic follow-up may lead to either missed or delayed diagnosis of malignancy. Moreover, periodic endoscopic checkups can be stressful and troublesome for patients. Therefore, when SETs suspected to be GISTs are identified using various diagnostic tools, endoscopic resection (ER) is an option for definitive histopathological diagnosis, as well as complete removal.

For localized gastric GISTs, surgical resection (SR) is the treatment of choice. With the advancements in ER techniques and the introduction of procedures, such as endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), and endoscopic full-thickness resection (EFTR), numerous attempts to treat gastric GISTs endoscopically have been made. In a recent study conducted at our center, ER was proven to be an effective and comparable treatment choice to SR for removing gastric GISTs <5 cm. In this study, two forms of ER were used: a standard ESD approach and a modified EFTR method used to cater to the procedure’s limitations. We devised a modified EFTR called “clip-assisted EFTR (cc-EFTR)” to facilitate the removal of gastric SETs located in the deep layer, similar to the EFTR technique. Furthermore, cc-EFTR was used for the treatment of areas that were difficult to access or resect with traditional ESD. This study evaluated the feasibility of ER and compared the clinical outcomes of ESD and cc-EFTR to determine the efficacy of the cc-EFTR method.

METHODS

Patient selection
This single-center, retrospective longitudinal cohort study included patients who underwent ER therapy for gastric GISTs at the Asan Medical Center, Seoul, Korea. Between June 2005 and December 2021, 104 patients underwent ER for SETs <5 cm in size, which were confirmed to be GISTs by clinical pathologists. During the same period, 1,011 patients underwent therapeutic procedures for gastric SETs, of which 637 patients received surgical treatment and 270 patients received ERs for SETs other than GISTs. In our center, follow-up was preferentially performed in cases of gastric SETs with an initial size of ≤25 mm. Additionally, ER was attempted if the SET was suspected to be a gastric GIST, a change in size or shape was observed, or the patient strongly wanted ER instead of surgical removal. Patients with clinicopathological data that could not be graded according to the modified 2008 National Institute of Health (NIH) consensus criteria, those who underwent ER techniques other than ESD or cc-EFTR, those who had no pre-treatment endoscopic ultrasonography (EUS) data, and those with GISTs >25 mm on initial EUS imaging were excluded. Thus, the data of 83 patients were analyzed. The flowchart of patient inclusion
is displayed in Figure 1.

Data collection
All patients’ clinical and pathological data were obtained and analyzed from medical records, including endoscopic and EUS images, final pathological reports, endoscopy record sheets, operation reports, hospital stay, and individual information. Moreover, EUS was utilized to evaluate the characteristics of SETs, including the initial and final size (last measured size before the procedure), echogenicity and homogeneity, the presence or absence of cystic foci and hyperechoic foci, which are associated with the malignant nature of GISTs.11,12 All eligible patients underwent esophagogastroduodenoscopy (EGD) and EUS before treatment. The type of ER procedure chosen depended on the endoscopists’ decision. Risk stratification of gastric GIST was evaluated according to the modified NIH consensus criteria.7,10

Endoscopic resection protocols
Until 2014, ESD was mainly performed for gastric SETs. However, after the development of cc-EFTR in 2014, endoscopists exercised discretion in selecting the treatment method, opting for either ESD or cc-EFTR. The choice was based on the location and characteristics of the lesion. All procedures were performed under conscious sedation with intravenous administration of 0.05 to 0.1 mg/kg of midazolam or 0.5 to 1 mg/kg of propofol, and 1.5 L/min of room air was insufflated through the endoscope. We used normal saline mixed with indigo carmine and a small amount of 0.005% epinephrine to lift the submucosal space of the lesion. A transparent cap (D-201-11814; Olympus) was applied at the tip of the forward-viewing single-chan-

![Flowchart of patient inclusion](image)

**Fig. 1.** Flowchart of patient inclusion. SET, subepithelial tumor; ER, endoscopic resection; GIST, gastrointestinal stromal tumor; NIH, National Institute of Health; STER, submucosal tunneling endoscopic resection; EUS, endoscopic ultrasonography; ESD, endoscopic submucosal dissection; cc-EFTR, clip-and-cut endoscopic full-thickness resection.
channel endoscope (GIF-H260 or GIF-HQ290; Olympus). Before the ER, we observed the lesion using white-light endoscopy and narrow-band imaging to determine the location. Insulated-tip knife-2 (KD-611L; Olympus), dual knife J (KD-655L; Olympus), and/or hook knife (KD-620LR; Olympus) were used to remove the SETs. Hemostatic clips (HX-610; Olympus) or RAICHO2 forceps (RC1550-2WE; Kaneka Medix) were used to control bleeding during the procedure.

ESD was performed following the conventional technique: lesion border marking, submucosal injection, circumferential incision, and submucosal dissection (Fig. 2A–H). In the cc-EF-TR method, following marking and submucosal injection, the operator attached a clip with dental floss to the edge of the dissected flap (Fig. 2I–P). The operator next retrieved the dental floss with the endoscope and reinserted the endoscope into the stomach while tugging with sufficient force to enable adequate visualization of the submucosal space and to prevent tearing the mucosal layer of the flap. In the process of partially dissecting the submucosal layer and identifying the muscularis propria (MP) layer that contained the SET, the operator made a small incision in the MP layer and approached the tumor. Before dissecting the MP layer, two to four sentinel clips were placed at both ends of the excision site to anchor the MP layer and prevent the transmural hole from enlarging. After meticulously dissecting the submucosal layer, the operator made a crescent-shaped transmural incision following the direction, in which each sentinel clip was attached, and evaluated the intra-abdominal structures by pulling the traction to ensure the transmural dissection was done. Transmural excision was performed gradually while continually dragging the traction and SET into the gastric cavity, and clips were used to preventatively suture the dissected area. This preventive clipping just after the transmural cut was repeated stepwise throughout the procedure until the entire dissected section was completely sutured. Then, the SET was captured inside the stomach, except for a very narrow connection with the MP layer. Once the perforated MP layer was adequately sutured, the final attachment to the remaining muscle layer was severed. After additional clipping at the excision site to confirm that the muscle layer was securely sutured, the specimen was retrieved, and the procedure was completed (Supplementary Video 1).

**Histopathological evaluation**
The specimens were processed with hematoxylin and eosin staining for evaluation. Immunohistochemical (IHC) staining for cluster of differentiation (CD) 117 (c-kit), CD34, desmin, smooth muscle actin, Ki-67, and S-100 was employed. Positive results in each IHC staining were regarded as confirmation of GIST. The tumor size and mitotic count per 50 high-power fields (HPFs) of each specimen were evaluated by clinical pathologists. These results were used for risk stratification of gastric GIST based on the modified NIH consensus criteria. 

**Follow-up protocols after ER**
Chest radiographs were performed on all the patients to assess for adverse events, such as pneumothorax and pneumoperitoneum after the procedure. On hospitalization day 2 or 3, a follow-up EGD was performed. Patients who did not experience post-ER adverse events were discharged as their diet progressed. Proton pump inhibitors were administered for 2 to 4 weeks after the procedure to prevent delayed bleeding. EGD and abdominal computed tomography (CT) were performed annually for 5 years.

**Definitions**
The location of gastric GISTs was classified into upper, middle, and lower parts of the stomach. The upper part included the fundus, cardia, and high body; the middle part included the mid and lower body; and the lower part included the gastric angle and antral portion. The resection margins were evaluated by clinical pathologists. We divided the SETs according to the extent of MP layer involvement (e.g., none, <50%; involved ≥50%; and outside of MP), as evaluated by the EUS performed by expert endoscopists. An R0 resection was defined as no gross or microscopic tumor remaining in the primary tumor bed with a negative resection margin. Complete resection was referred to as R0 resection. An R1 resection was defined when remnant tumor cells were observed microscopically on the resection margin. Additionally, an R2 resection was defined as gross remnant tumors. Peritonitis was defined as a case accompanied by both rebound tenderness of the abdominal wall in physical examination and the presence of fever (≥38 °C of the body temperature) after the procedure. The procedure time was defined as the duration between the beginning of marking and the extraction of the SETs through the mouth.

**Statistical analysis**
Baseline characteristics between the ESD and cc-EFTR groups were compared. Quantitative data, such as age, tumor size, procedure time, and hospital stay, were expressed as medians.
Fig. 2. (A–H) Case illustration of endoscopic submucosal dissection. (A) A subepithelial tumor (SET) in the distal antrum. (B) After marking around the lesion with an endoscopic knife, submucosal injection is administered. (C–F) Circumferential incision followed by submucosal dissection is performed. (G) After removing the SET, hemostasis is performed with coagulation forceps. (H) The removed gastric SET is displayed. (I–P) Case illustration of clip-and-cut endoscopic full-thickness resection. (I) A SET in the fundus is displayed. (J) Submucosal injection and circumferential incision are performed. (K) A clip with dental floss is applied to the mucosa above the SET for traction. (L) Sentinel clips are placed on both sides of the resected area to anchor the muscularis propria layer. (M) Transmural resection is performed using continuous traction to pull the SET into the stomach. (N) Transmural resection and perforation closure with clips are carried out simultaneously. (O) After the SET is completely excised, additional clipping is performed to strengthen the closure site. (P) The removed gastric SET is displayed.

with interquartile ranges (IQRs). Qualitative data, such as sex, symptoms, location, shape, pathological grade of tumor, and resection rate were expressed as proportions. Categorial variables were compared in non-parametric tests using the Kruskal-Wallis test. A probability level ($p$) of 0.05 was chosen for statistical significance. Univariate and multivariate analyses were per-
formed in addition to logistic regression analysis with backward elimination. All statistical analyses were performed using IBM SPSS Statistics for Windows ver. 21.0 (IBM Corp.) and Prism 9 for Windows ver. 9.3.1 (GraphPad Software Inc.).

**Ethical concerns**

Ethical approval for the acquisition of data was obtained from the Institutional Review Board (IRB) of the Asan Medical Center (No. 2020-0957). Additionally, due to the retrospective nature of the study, the IRB waived the need for informed consent.

**RESULTS**

**Baseline patient characteristics**

The baseline patient characteristics are displayed in Table 1. Among 83 patients who underwent therapeutic ER procedures for gastric GIST, ESD and cc-EFTR were performed in 51

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=83)</th>
<th>ESD (n=51)</th>
<th>cc-EFTR (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (39.8)</td>
<td>19 (37.3)</td>
<td>14 (43.8)</td>
<td>0.559</td>
</tr>
<tr>
<td>Female</td>
<td>50 (60.2)</td>
<td>32 (62.7)</td>
<td>18 (56.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.0 (51.0–68.0)</td>
<td>58.0 (51.0–66.0)</td>
<td>64.0 (53.3–69.8)</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>Follow-up period (month)</strong></td>
<td>25.0 (13.0–49.0)</td>
<td>29.0 (13.0–85.0)</td>
<td>24.5 (12.3–37.8)</td>
<td>0.211</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper third</td>
<td>56 (67.5)</td>
<td>27 (52.9)</td>
<td>29 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Middle third</td>
<td>16 (19.3)</td>
<td>14 (27.5)</td>
<td>2 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Lower third</td>
<td>11 (13.3)</td>
<td>10 (19.6)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial EUS size (mm)</strong></td>
<td>15.8 (11.3–19.4)</td>
<td>15.7 (12.0–20.0)</td>
<td>16.0 (10.0–19.2)</td>
<td>0.597</td>
</tr>
<tr>
<td><strong>Final EUS size (mm)</strong></td>
<td>19.0 (14.8–22.3)</td>
<td>20.0 (15.0–23.0)</td>
<td>17.9 (13.0–20.6)</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>Indication of ER</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.480</td>
</tr>
<tr>
<td>Highly suspicious of GIST</td>
<td>28 (33.7)</td>
<td>16 (31.4)</td>
<td>12 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Change of size or shape</td>
<td>45 (54.2)</td>
<td>28 (54.9)</td>
<td>17 (53.1)</td>
<td></td>
</tr>
<tr>
<td>Refusal of surgery</td>
<td>10 (12.0)</td>
<td>7 (13.7)</td>
<td>3 (9.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Echogenicity</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.851</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>80 (96.4)</td>
<td>49 (96.1)</td>
<td>31 (96.9)</td>
<td></td>
</tr>
<tr>
<td>Mixed echoic</td>
<td>3 (3.6)</td>
<td>2 (3.9)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Homogeneity</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.480</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>64 (77.1)</td>
<td>38 (74.5)</td>
<td>26 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Inhomogeneous</td>
<td>19 (22.9)</td>
<td>13 (25.5)</td>
<td>6 (18.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperechoic foci</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.899</td>
</tr>
<tr>
<td>None</td>
<td>68 (81.9)</td>
<td>42 (82.4)</td>
<td>26 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (18.1)</td>
<td>9 (17.6)</td>
<td>6 (18.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Cystic foci</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>None</td>
<td>75 (90.4)</td>
<td>49 (96.1)</td>
<td>26 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (9.6)</td>
<td>2 (3.9)</td>
<td>6 (18.8)</td>
<td></td>
</tr>
<tr>
<td><strong>MP involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>1 (1.2)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>28 (33.7)</td>
<td>27 (52.9)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>19 (22.9)</td>
<td>11 (21.6)</td>
<td>8 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Outside of MP</td>
<td>35 (42.2)</td>
<td>12 (23.5)</td>
<td>23 (71.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gross morphology</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>38 (45.8)</td>
<td>27 (52.9)</td>
<td>11 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Semi-pedunculated</td>
<td>31 (37.3)</td>
<td>19 (37.3)</td>
<td>12 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Sessile</td>
<td>14 (16.9)</td>
<td>5 (9.8)</td>
<td>9 (28.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range).

GIST, gastrointestinal stromal tumor; ESD, endoscopic submucosal dissection; cc-EFTR, clip-and-cut endoscopic full-thickness resection; EUS, endoscopic ultrasonography; MP, muscularis propria.
(61.4%) and 32 (38.6%) patients, respectively. The incidence of gastric GISTs was high in the upper body (52.9% for ESD vs. 90.6% for cc-EFTR, p<0.001). Compared to the cc-EFTR, the number of GISTs containing cystic foci was higher in the ESD group (96.1% for ESD vs. 81.3% for cc-EFTR, p=0.027). In comparison to the ESD group, gastric GISTs treated with cc-EFTR exhibited a higher percentage of lesions situated outside of the MP layer (23.5% for ESD vs. 71.9% for cc-EFTR, p<0.001). Additionally, the shapes of these lesions were less protruding (52.9% for ESD vs. 34.4% for cc-EFTR, p=0.035).

**Clinical outcomes**

The endoscopic results of each method are described in Table 2. Overall, 79.5% of gastric GIST demonstrated very low and low-risk tumor grades, and the overall R0 and R1 resection rate was 91.6%. To determine the differences based on the location, in treatment outcomes of each method, we divided the location of the lesion into two categories: upper third, and the middle plus lower third (Fig. 3). In the upper third, the cc-EFTR group exhibited a higher R0 resection rate than the ESD group (44.4% for ESD vs. 86.3% for cc-EFTR, p=0.001) without a significant difference in the procedure time (28.0 minutes for ESD vs. 39.0 minutes for cc-EFTR, p=0.109). However, in the middle plus lower third, neither the resection margin (58.3% for ESD vs. 66.7% for cc-EFTR, p=0.437) nor the procedure time (27.0 minutes for ESD vs. 40.0 minutes for cc-EFTR, p=0.449) displayed any significant differences between two methods. During univariate and multivariable analysis associated with R0 resection, ER with cc-EFTR method (odds ratio [OR], 5.192; 95% confidence interval [CI], 1.727–15.613; p=0.03) was discovered to be an independent predictive factor of R0 resection (Table 3). Five patients in the ESD group underwent additional staged surgical treatments after the ERs. The patients underwent additional SR due to R2 resection (four patients with wedge resection and one patient with total gastrectomy). The summary of patients who underwent staged additional surgeries after ERs are presented in Table 4.

**Table 2. Clinical outcomes of the ER methods**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=83)</th>
<th>ESD (n=51)</th>
<th>cc-EFTR (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stays (day)</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (4.0–6.0)</td>
<td>0.926</td>
</tr>
<tr>
<td>Pathologic size (mm)</td>
<td>20.0 (15.0–24.0)</td>
<td>21.0 (16.0–25.0)</td>
<td>19.0 (15.0–22.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>Mitosis, per 50 HPF</td>
<td></td>
<td></td>
<td></td>
<td>0.676</td>
</tr>
<tr>
<td>≤5</td>
<td>65 (78.3)</td>
<td>41 (80.4)</td>
<td>24 (75.0)</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>15 (18.1)</td>
<td>7 (13.7)</td>
<td>8 (25.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>3 (3.6)</td>
<td>3 (5.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade(^a)</td>
<td></td>
<td></td>
<td></td>
<td>0.172</td>
</tr>
<tr>
<td>Very low risk</td>
<td>36 (43.4)</td>
<td>18 (35.3)</td>
<td>18 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>30 (36.1)</td>
<td>23 (45.1)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>14 (16.9)</td>
<td>7 (13.7)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>3 (3.6)</td>
<td>3 (5.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Resection margin</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>R0</td>
<td>53 (63.9)</td>
<td>26 (51.0)</td>
<td>27 (84.4)</td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>23 (27.7)</td>
<td>19 (37.3)</td>
<td>4 (12.5)</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>7 (8.4)</td>
<td>6 (11.8)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>33.0 (21.0–51.0)</td>
<td>28.0 (20.0–46.0)</td>
<td>39.5 (30.5–54.8)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

ER, endoscopic resection; ESD, endoscopic submucosal dissection; cc-EFTR, clip-and-cut endoscopic full-thickness resection; HPF, high-power field.

\(^a\)Tumor grade was based on modified National Institute of Health consensus criteria, 2008.

**Adverse events**

A total of 43 (51.8%) patients experienced adverse events after ER (Table 5). The overall rates of adverse events were higher in the cc-EFTR group compared to that in the ESD group (37.3% for ESD vs. 75.0% for cc-EFTR, p=0.001). Pneumoperitoneum occurred in 13 (25.5%) and 22 (68.8%) patients in the ESD and cc-EFTR groups, respectively. However, only one patient in the ESD group and two in the cc-EFTR group progressed to localized peritonitis, however, they recovered after conservative care, including broad-spectrum antibiotic administration (2.0% for ESD vs. 6.3% for cc-EFTR, p=0.311). Two patients underwent emergent operations during the ER. In the ESD group, a patient with severe bleeding during the procedure underwent emergent wedge resection. In the cc-EFTR group, a patient with failed en-
endoscopic closure for a huge transmural hole during ER underwent emergent wedge resection. All other patients were managed with conservative treatment, including endoscopic closure with hemostatic clips and intravenous antibiotics, without any further adverse events. A summary of patients who underwent surgical procedures after ERs due to endoscopic adverse events is displayed in Table 4.

Fig. 3. Differences between the resection margin status and procedure time according to location. To investigate the efficacy of endoscopic submucosal dissection (ESD) and clip-and-cut endoscopic full-thickness resection (cc-EFTR) according to location, the state of resection margin and procedure time are compared between the upper third and middle plus lower third groups. Unlike the middle plus lower third group, which had no differences in resection margin and procedure time, the R0 resection rate is significantly high in cc-EFTR in the upper third groups. (A, B) Resection margin status of upper third and middle plus lower third. (C, D) Procedure time of upper third and middle plus lower third.
Table 3. Univariate and multivariable analysis associated with R0 resection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.944 (0.780–4.850)</td>
<td>0.154</td>
</tr>
<tr>
<td>Age</td>
<td>1.020 (0.978–1.065)</td>
<td>0.352</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low to low</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate to high</td>
<td>1.463 (0.461–4.648)</td>
<td>0.518</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper third</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Middle to lower third</td>
<td>0.747 (0.290–1.924)</td>
<td>0.546</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedunculated</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Semi-pedunculated</td>
<td>1.890 (0.705–5.067)</td>
<td>0.094</td>
</tr>
<tr>
<td>Sessile</td>
<td>5.400 (1.061–27.472)</td>
<td>0.048</td>
</tr>
<tr>
<td>MP involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>2.217 (0.871–5.639)</td>
<td>0.095</td>
</tr>
<tr>
<td>Pathologic size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 mm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥25 mm</td>
<td>0.353 (0.126–0.992)</td>
<td>0.048</td>
</tr>
<tr>
<td>Procedure method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESD</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>cc-EFTR</td>
<td>5.192 (1.727–15.613)</td>
<td>0.003</td>
</tr>
<tr>
<td>Procedure time</td>
<td>0.989 (0.969–1.009)</td>
<td>0.272</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; MP, muscularis propria; ESD, endoscopic submucosal dissection; cc-EFTR, clip-and-cut endoscopic full-thickness resection.

Table 4. Summary of patients who underwent surgical procedures after ER

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex/age (y)</th>
<th>Method of ER</th>
<th>Location</th>
<th>Indication for surgery</th>
<th>Method of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male/51</td>
<td>ESD</td>
<td>Middle third</td>
<td>R2 resection</td>
<td>Staged WR</td>
</tr>
<tr>
<td>2</td>
<td>Male/49</td>
<td>ESD</td>
<td>Upper third</td>
<td>R2 resection</td>
<td>Staged TG</td>
</tr>
<tr>
<td>3</td>
<td>Female/59</td>
<td>ESD</td>
<td>Middle third</td>
<td>R2 resection</td>
<td>Staged WR</td>
</tr>
<tr>
<td>4</td>
<td>Female/63</td>
<td>ESD</td>
<td>Middle third</td>
<td>Bleeding</td>
<td>Emergent WR</td>
</tr>
<tr>
<td>5</td>
<td>Female/54</td>
<td>ESD</td>
<td>Upper third</td>
<td>R2 resection</td>
<td>Staged WR</td>
</tr>
<tr>
<td>6</td>
<td>Male/72</td>
<td>cc-EFTR</td>
<td>Upper third</td>
<td>Gross perforation</td>
<td>Emergent WR</td>
</tr>
<tr>
<td>7</td>
<td>Female/53</td>
<td>ESD</td>
<td>Upper third</td>
<td>R2 resection</td>
<td>Staged WR</td>
</tr>
</tbody>
</table>

ER, endoscopic resection; ESD, endoscopic submucosal dissection; WR, wedge resection; TG, total gastrectomy; cc-EFTR, clip-and-cut endoscopic full-thickness resection.

Table 5. Characteristics of the adverse events of the ER procedures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=83)</th>
<th>ESD (n=51)</th>
<th>cc-EFTR (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>20 (24.1)</td>
<td>7 (13.7)</td>
<td>13 (40.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>35 (42.2)</td>
<td>13 (25.5)</td>
<td>22 (68.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>3 (3.6)</td>
<td>1 (2.0)</td>
<td>2 (6.3)</td>
<td>0.311</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Oncologic outcomes
The median follow-up period for all patients was 25.0 months. One patient in the ESD group experienced GIST recurrence. A 77-year-old man with underlying metastatic prostate cancer was incidentally diagnosed with a 22 mm-sized GIST in the lower body during his routine EGD examination. After 4-year follow-up, the SET increased in size to 26 mm, leading to the
decision to undergo ESD. The pathological results displayed an intermediate risk for gastric GIST according to the modified NIH criteria. The resection margin was clear in the final clinicopathological report, and his serial follow-up EGD displayed no residual tumor. After 4 years of ER, a 28 mm-sized recurrent exophytic GIST was observed in the high body of the stomach on follow-up CT images. Considering the patient’s age and performance status, the patient was observed without additional ER or SR. The patient died 17 months after diagnosis of a recurrent tumor due to the progression of prostate cancer.

One patient in the cc-EFTR group received adjuvant chemotherapy with the tyrosine kinase inhibitor, imatinib. A 75-year-old man underwent cc-EFTR for a 19.2 mm-sized gastric GIST with a mitotic count of 10/50 HPFs; therefore, he was categorized as an intermediate-risk group patient according to the modified NIH criteria. However, as the mitotic count was 10/50 HPF and the risk of recurrence was relatively high in the groups with indeterminate risk, adjuvant imatinib chemotherapy was initiated after consultation with the oncologist. After 5 days, he experienced angioedema as a side effect of imatinib, due to which he stopped the chemotherapy. Subsequent follow-ups through the outpatient clinic displayed no evidence of recurrence. These results are summarized in Figure 4.

**DISCUSSION**

The procedure of cc-EFTR was developed to overcome the limitations of EFTR, reduce the size of muscle defect at the time of closure, and reduce the procedure time. In our study, we compared the efficacy of ER and the safety of the cc-EFTR and ESD methods in removing small gastric GISTs. We discovered that ER demonstrated R0 and R1 resection rates of 63.9% and 27.7%, respectively, and during the 25 months follow-up period, only one patient experienced recurrence after ER. Specifically, cc-EFTR demonstrated a significantly high R0 resection rate, especially in the upper part such as the fundus, cardia, and high body. Despite the high incidence of adverse events compared to the ESD group, all but one patient, who underwent emergent surgery during the procedure, were managed with conservative care, indicating that the cc-EFTR method can be one of the possible options for removing gastric GISTs.

Although SR is the standard treatment for gastric GISTs in the National Comprehensive Cancer Network guideline and endoscopic treatment is not widely recommended owing to the
lack of long-term safety, several studies have suggested ER as an alternative therapeutic option. Our previous study compared the safety and efficacy of ER and SR for small gastric GISTs <5 cm. Statistically, the R0 resection rate for ER was 60.8%, which was lower than that for SR (98.5%); nevertheless, no tumor recurrence was observed during the 47.9 months follow-up period. Joo et al. also evaluated the feasibility and long-term outcomes of ER against SR. In the ER group, tumor size was smaller and the R0 resection rate was lower compared to that in the SR group (25.0% vs. 85.0%). However, no significant difference in the recurrence rate was observed during the 45.5 months follow-up period, consistent with our findings. In this study, the R0 resection rate was 63.9% and confirmed as 84.4% in the cc-EFTR group, equivalent to the R0 resection rate in the surgical group confirmed in the prior studies.

Although the R0 resection rate of ER was lower than that of SR in previous reports, no patients undergoing R1 and R2 resection in the cc-EFTR group experienced recurrence. Unlike those undergoing R2 resection, the majority of those undergoing R1 resection did not receive surgery, and despite the follow-up observation, no recurrence or metastasis was observed. R1 resection may not indicate an incomplete excision; rather, it could be a result according to the three-dimensional characteristics of GISTs. GISTs are enveloped by a pseudocapsule and necessitate en bloc enucleation to prevent tumor spillage. In contrast to flat lesions, such as adenomas or cancers, the pathological evaluation of the resection margin of GISTs with a three-dimensional structure surrounded by pseudocapsules might be difficult to evaluate precisely because of tissue deformation during sectioning and chemical fixation. Therefore, R1 resection does not always indicate incomplete resection owing to the possibility of false-positive margins. Moreover, en bloc resections were performed in all 83 procedures of the present study; thus, the potential for post-procedural adverse events, such as peritoneal seeding, was minimal or negligible. Several studies have investigated the impact of R1 resection on the prognosis of gastric GISTs, including the recurrence of the GISTs. A study conducted by McCarter et al. in 2012 revealed that 72 (8.8%) out of the 819 patients who underwent SR of gastrointestinal GISTs had an R1 resection status. Moreover, no significant differences were observed in recurrence-free survival between the R0 and R1 groups, regardless of the administration of adjuvant imatinib (p=0.73) or placebo (p=0.24). Additionally, a study by Joo et al. in 2016 involved the endoscopic removal of GISTs in the upper gastrointestinal (GI) tract in 90 patients, among whom pathological R1 resection was confirmed in 65 individuals (72.2%). Throughout a median follow-up period of 45.5 months, only two patients in the R1 resection group experienced recurrence. Furthermore, a study by Zhu et al. in 2020 analyzed the relationship between the status of the resection margin and the recurrence rate of gastrointestinal mesenchymal tumors (GIMTs), including GISTs in the stomach. The R1 resection group of gastric GIMTs did not experience a higher recurrence rate than the R0 resection group (p=0.84).

In terms of adverse events, more patients had post-procedure fever and pneumoperitoneum after undergoing cc-EFTR than those undergoing ESD. Although room air, not carbon dioxide gas, was used throughout the endoscopic procedure and the procedure was performed under conscious sedation, not under general anesthesia, no changes in vital signs accompanied pneumoperitoneum during or after the procedure. This observation is similar to that of postoperative pneumoperitoneum, which is a benign condition that spontaneously remits and is seen as an unavoidable consequence of transmural excision of deeply seated tumors. Only one patient underwent emergent surgery immediately after the cc-EFTR procedure. The site that underwent transmural resection was left without clip closure due to challenges in positioning. This area was specifically the junction between the greater curvature and the posterior wall side of the upper body. Except for one patient who underwent surgical conversion during cc-EFTR, all patients were successfully treated primarily using endoscopic clips, and none of the patients with pneumoperitoneum in post-procedural radiographs progressed to life-threatening peritonitis.

In our study, GISTs were mainly removed using ESD or cc-EFTR, and the complete resection rate was significantly higher in the cc-EFTR group than that in the ESD group. Additionally, ESD can be an effective ER method, but the applicability of the procedure is limited as it is beneficial mainly on SETs with narrow connections with the MP layer. Bialek et al. retrospectively analyzed the clinical outcomes of ESD for 37 patients with SETs, including 17 (46%) with gastric GISTs, and a difference in the complete resection rate was observed according to the connection with the MP (100% in SETs with no connection vs. 68.2% in SETs with connection). An et al. also evaluated the feasibility of ESD in removing gastric GISTs, as well as the risk factor of a gastric wall defect. The risk of perforation was high when the surface connecting to the MP was wide or the lesion extended below the MP layer. In our data, 28 (54.9%) tumors demonstrated none or <50% MP in-
volvement, and 27 (52.9%) tumors had a pedunculated shape in the ESD group, indicating that the technique was more often performed for superficially located lesions. In the cc-EFTR group, however, 31 (96.9%) tumors had ≥50% MP involvement and the morphology of the SETs were not confined, suggesting cc-EFTR may be beneficial for gastric GISTs with a wide range of shape and location. Moreover, the R0 resection rate was high in lesions located in the upper third. This is considered clinically significant, as determining the exact shape and location of gastric GISTs using EUS alone is difficult. The procedural difficulty, which is thought to be associated with the location and depth of the SETs, may be relieved by continuously drawing the SETs into the gastric cavity using a clip, where dental floss is attached throughout the process.

In conventional EFTR, wall repair with a suture/clip device or laparoscope may be necessary if the size of the stomach wall perforation generated after the transmural dissection of the entire gastric layers is too large to be managed by hemoclips.\(^{20,21}\) In this study, we used the hemostatic clips to seal the hole during every small transmural cut, which is readily available in most situations. Universality is an advantage when using a clip to seal a hole as it is easy to use, can be utilized at any moment during the procedure, does not require additional device installation, and can be utilized in the majority of endoscopic centers. Various novel devices, such as over-the-scope clips (OTSCs) and endoscopic suturing devices were developed and utilized in removing gastric SETs.\(^{22-25}\) Although these devices were designed to securely and easily close the transmural perforation site, they are only used in a limited number of endoscopic centers, and their high cost is a drawback. In OTSC, transmural resection of SETs, as well as closing perforation site is available. However, as the procedure with OTSC is conducted without visually checking the deep resection margin, a danger persists of remnant tumors after resection. Throughout the simple repetition of closing processes with the clips, the cc-EFTR displayed advantages in an easy approximation of the resected lesion and non-inferior results in the procedure time compared to ESD.

Our study only investigated ESD or cc-EFTR, not STER, as the number of clinical situations where STER could be applied was quite limited. Furthermore, STER has been used as a good option for removing SETs as the procedure can promote rapid wound healing and further decrease adverse event rates, ever since the first clinical report by Inoue et al.\(^{26}\) A systemic review and meta-analysis also reported both high complete (97.5%) and en bloc (94.6%) resection rates for STER.\(^{27}\) However, STER may be difficult to perform clinically in many instances, hence the number of cases in which STER was performed in our institution was extremely low and excluded from the study. During the STER procedure, the operator must form a submucosal tunnel using an endoscopic knife to remove gastric GISTs located in the deep MP layer; however, procedure time increased in this process. Additionally, laceration or perforation of the gastric mucosal layer can occur during submucosal tunnel formation in patients with a moderate to severe degree of atrophic change in the gastric mucosa. Moreover, the application of STER to lesions situated in challenging areas of the stomach, where forming a tunnel is difficult due to the polygonal shape, such as the gastric fundus and lesser curvature, poses a challenge. This difficulty could potentially result in serious adverse events.

This study had certain limitations. First, as this was a retrospective, observational, and single-center study, the results may have been limited. Given these points, the patient population might be limited; furthermore, the decision to introduce an endoscopic treatment regimen of gastric SETs was based on the physician’s discretion, which might have introduced bias. Additionally, as the cc-EFTR method was devised in 2014, the follow-up duration may be short. Thirdly, because endoscopic resection of gastric SET is challenging for novice therapeutic endoscopists and requires sufficient experience with endoscopic procedures to competently perform, the risks of the procedure may have been relatively understated. Furthermore, even though the price is less than that of other suture devices, such as OTSCs, additional expenses may be incurred when using clips or dental floss. Finally, the cc-EFTR group required a longer procedure duration than the ESD group. To accurately evaluate the duration of each procedure, lesions in comparable locations should be compared. Nevertheless, in this study, the preferred endoscopic treatment varied depending on the location of the lesion, which might have affected the study findings. Therefore, considering the outcomes of this study, a future multi-center, long-term follow-up prospective study should be conducted to evaluate the efficacy of cc-EFTR more comprehensively. Despite these limitations, our study results suggest that ER is a safe and feasible method for gastric SETs and that the cc-EFTR method was feasible for GISTs in terms of curability and safety, especially when located in the fundus, cardia, and high body.

In conclusion, ER seems to be a safe and effective therapeutic option for the removal of gastric GISTs. The cc-EFTR method in removing GIST transmurally exhibited a higher R0 resection rate, which was useful and safe for complete resection, even in...
areas where ESD cannot be easily performed.

**Supplementary Material**

**Supplementary Video 1.** Procedure of clip-and-cut endoscopic full-thickness resection method.

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.14.

**Conflicts of Interest**

Supplementary Video 1 included in this paper is a partially modified version of a case that was presented at the DDW’s video forum in 2017. Ji Yong Ahn is currently serving as a section editor for Clinical Endoscopy; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. The other authors have no potential conflicts of interest.

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**Author Contributions**

Conceptualization: YK, JYA, HYJ; Data curation: all authors; Formal analysis: YK, JYA; Supervision: HYJ; Writing–original draft: YK, JYA; Writing–review & editing: all authors.

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**REFERENCES**


Comparison of 19-gauge conventional and Franseen needles for the diagnosis of lymphadenopathy and classification of malignant lymphoma using endoscopic ultrasound fine-needle aspiration

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Both 19-G needles showed high accuracy. Considering the sufficient tissue collection and avoidance of AEs, use of 19-G conventional needles seems to be a good option for lymphadenopathy diagnosis.
INTRODUCTION

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is an accurate and safe procedure for diagnosing unknown mediastinal or abdominal masses and lymphadenopathy.1-4 To diagnose lymphadenopathy, large tissue samples are required for a pathological assessment, which includes immunohistochemistry, flow cytometry, and a cytogenetic assessment. The use of a large-gauge (19-gauge, 19-G) needle has enabled the sampling of large amounts of tissue from lymphadenopathy.5 Recently, Franseen needles have been reported to be useful for tissue sampling of pancreatic and subepithelial lesions6-9; additionally, 19-G Franseen needles seem to be suitable for obtaining large tissue samples. However, the efficacy of diagnosing lymphadenopathy using the 19-G Franseen needle remains unclear. This study aimed to compare the effectiveness of 19-G conventional and Franseen needles in the diagnosis of lymphadenopathy and classification of malignant lymphoma (ML).

METHODS

Patients
This retrospective study was conducted at the Gifu Municipal Hospital, where more than 100 EUS-FNA procedures are performed annually. The patient database, including clinical data of EUS-FNA performed between January 2012 and February 2022, was searched. The inclusion criteria were as follows: (1) age >20 years, (2) lymphadenopathy, and (3) use of a 19-G needle. The exclusion criteria were (1) use of needles other than the 19-G needle, (2) inability to provide informed consent, and (3) an individual considered ineligible by the investigators.

EUS-FNA procedure
EUS-FNA was performed using an oblique forward-viewing electronic linear scanning video echoendoscope (GF-UC240AL-5, or GF-UCT 260; Olympus Optical). The echoendoscope was inserted into the patient while in the left lateral decubitus position. After visualizing the lymph node (LN), Doppler mode was used to confirm blood flow to avoid puncturing the vessel with the aspiration line. Following the EUS evaluation, a puncture was performed under EUS guidance via the esophageal, gastric, or duodenal wall (Fig. 1A). Our institution is a core hematology hospital; therefore, many patients with lymphadenopathy suspected of having ML visit our hospital. Therefore, EUS-FNA is typically performed using a 19-G needle to obtain sufficient tissue samples, considering the wide range of pathological examinations. The needle was advanced to the LN and the stylet was removed. The needle was passed back and forth 10 times in the LN with a 10 mL syringe suction. The puncture session continued until sufficient whitish material was obtained for pathological examination. One or two additional punctures were made to obtain a sufficient amount of material. These samples were divided into two tubes containing RPMI 1640 medium, one for flow cytometry and the other for cytogenetic assessment.

Rapid on-site evaluations
Rapid on-site evaluation (ROSE) was performed by a cytopa-
Fig. 1. The process of lymphadenopathy and malignant lymphoma diagnosis using a 19-gauge conventional or Franseen needle. (A) Endoscopic ultrasound (EUS) fine needle aspiration performed under EUS guidance in Doppler mode. (B) Cytology stained with Giemsa shows small, atypical lymphocytes. Scale bar=20 μm. (C) Histopathology shows a lymphoid follicle consisting of small, atypical lymphocytes. Scale bar=50 μm. (D) Immunohistochemical staining is positive in CD20, CD10, Bcl-2, and negative in CD3. (E) The flow cytometry analysis of this case shows the expression of B-cell lineage antigens (CD10, CD19, and CD20) and immunoglobulin light chains (κ). Scale bar=20 μm. (F) A G-banded karyotyping analysis finds t(14;18)(q32;q21) chromosomal translocation (arrows). (G) The fluorescence in situ hybridization assay of this case indicates a green signal for IGH, a red signal for BCL-2, and a yellow signal (arrows) for a fusion of IGH and BCL-2.
thologist/cytotechnologist in the procedural room for all EUS-FNA procedures. The EUS-FNA specimens were placed on glass slides and smeared for on-site preparation. Before staining, the obtained sample was gently placed on the side to avoid crushing the artifacts. Subsequently, each slide was air-dried for Diff-Quik staining. Finally, a cytopathologist or cytotechnologist determined whether the samples were positive (definitive cytopathological evidence of malignancy) or negative (no malignant cells), after which the samples were processed for further examination. EUS-FNA was performed until adequate tissue samples that could be analyzed using ROSE were obtained.

Pathological diagnosis, flow cytometry, cytogenetic assessment, and final diagnosis

The aspirated material was expelled onto a glass slide. A whitish portion of the material was cut and removed from the clot using tweezers. The collected whitish tissue was fixed in 10% neutral buffered formalin solution for pathological and immunohistochemical examinations. The remaining whitish samples were smeared onto glass slides for cytological examination (Fig. 1B). Finally, the material was embedded in paraffin wax and processed to prepare 3 to 4 mm-thick serial sections for hematoxylin-eosin staining and immunohistochemistry (Fig. 1C, D). Several monoclonal and polyclonal antibodies, including those against ML, have been used in immunohistochemistry to obtain an accurate pathological diagnosis of lymphadenopathy. Pathologists (YK, NW, and TT) independently made cytological and histopathological diagnoses. For ML, flow cytometry was performed using the following antibodies: B-cell lineage antigens CD10, CD19, CD20, and Bcl2; T-cell lineage antigens CD2, CD3, CD4, CD5, and CD7; additional antigens CD25, CD30, CD34, CD38, CD45, and CD56; and IgM, immunoglobulin light chains (k and λ) (Fig. 1E). Cytogenetic abnormalities were assessed using conventional G-banded karyotyping (Fig. 1F). A fluorescence in situ hybridization (FISH) assay was performed to determine the diagnosis in cases requiring a detailed clinical evaluation (Fig. 1G). The final diagnoses of ML, determined according to the World Health Organization (WHO) classification or metastasis of malignant lesions, were determined based on the pathological findings and clinical course. Benign diagnoses were confirmed when lymphadenopathy progression did not occur on follow-up imaging for ≥6 months.

Study endpoints and needle type

The study endpoint was to compare 19-G conventional and Franseen needles for diagnosing lymphadenopathy. Conventional (end-cut) 19-G needles (Echo Tip, Wilson-Cook; EZ shot3, Olympus; SonoTip Pro Control, Medi-Globe; Expect Slimline, Boston Scientific) were used frequently until December 2017 (conventional group), and Franseen needles (Acquire, Boston Scientific; SonoTip TopGain, Medi-Globe) were frequently used after January 2018 (Franseen group). The procedures and specimen handling methods were the same for both groups. The outcomes of both groups were compared to evaluate sensitivity (malignant), specificity (benign), positive predictive value (PPV), negative predictive value (NPV), and lymphadenopathy accuracy based on histological and cytological findings. As patients were diagnosed with ML, the sensitivity of the ML classification diagnostic examinations, including immunohistochemical evaluation of histological specimens, flow cytometry, and cytogenetic assessment, was compared between the two groups. Adverse events (AEs) after EUS-FNA were also compared.

Statistical analyses

All analyses were conducted using R ver. 4.0.2 (The R Foundation for Statistical Computing). Values are expressed as number of patients or median (range). Fisher exact test and the Mann-Whitney U-test were used for categorical and continuous variable analyses, respectively. A p-value <0.05 was considered statistically significant. Subgroup analyses were performed to evaluate the diagnostic yield of conventional and Franseen needle sampling for each lymphadenopathy puncture route. To identify the factors of accurate lymphadenopathy diagnostic performance, a logistic analysis was performed with an adjustment for clinically significant findings, including age, sex, lesion size, number of needle passes, needle type, and puncture route, on cytological or histological accuracy. Factors related to accurate lymphadenopathy diagnosis (p<0.20) in the univariate analysis were further assessed using multivariate analysis. The regression analysis results are expressed as odds ratios (ORs). Median values were used to determine the cut-off values for age, lesion size, and number of needle passes.

Ethics approval

This study was approved by the Institutional Review Board of Gifu Municipal Hospital (no. 749) and adhered to the Declaration of Helsinki. The study protocol was registered with the
University Hospital Medical Information Network Clinical Trials Registry (UMIN000046873).

RESULTS

Patient selection and characteristics
We enrolled 172 patients with lymphadenopathy who underwent EUS-FNA between January 2012 and February 2022. Out of this group, 26 were excluded based on eligibility criteria: a 22-G needle was used in 25 patients and a 25-G needle was used in one (Supplementary Tables 1, 2). A total of 146 patients met the inclusion criteria (conventional group, 70 patients; Franseen group, 76 patients) (Fig. 2). Among them, 110 were diagnosed with ML. Of the remaining participants, five had metastatic diseases (lung cancer [four patients] and gastric cancer [one patient]) and 31 benign cases (sarcoidosis [13 patients] and non-specific lymphadenopathy [18 patients]). Table 1 summarizes the baseline patient characteristics according to the WHO classification of ML cases. The median lesion size was 29 mm (range, 10–83 mm) in the conventional group and 34 mm (range, 12–110 mm) in the Franseen group, without statistical significance. Additionally, there were no significant differences between groups in terms of age, sex, lesion location, or final diagnosis.

Outcomes of EUS-FNA
The outcomes in both groups are shown in Table 2. There were no significant differences in the puncture routes. Tissue samples were obtained from both groups and evaluated using cytology and histology. The median number of needle passes was significantly higher in the Franseen group than in the conventional group (median [range]; 4 [1–6] vs. 3 [1–6] times, $p=0.023$). The occurrence of AEs was not significant; however, three cases of bleeding were observed in the Franseen group. There was one case of severe bleeding that required embolization following angiography after transesophageal puncture of the mediastinal LN (Fig. 3). There were no significant differences between the two groups in sensitivity, specificity, PPV, NPV, or accuracy for malignant diseases (ML and metastasis). To evaluate the factors related to diagnostic accuracy, the continuous variable factor was divided by the median values of 72 years of age, 32 mm lesion size, and four needle passes for logistic analysis. Based on the results of the univariate logistic analyses, the cytological factors of the female and Franseen groups were included in the multivariate analysis. However, no significant predictors for improved cytological accuracy were identified. No significant histological changes were identified either (Table 3).

Subgroup analysis of the lymphadenopathy diagnosis according to puncture route
The cytology and histology sensitivity, specificity, PPV, NPV, and accuracy were compared among the different puncture routes (esophageal, gastric, and duodenal) for lymphadenopathy (Table 4). No significant differences were observed between the two groups in any category for each puncture route.

Comparison of the needle type of diagnostic sensitivity for ML and WHO classifications
Overall, 110 (75.3%) of the 146 patients were diagnosed with ML. Table 5 summarizes the comparison of ML cases in 52 patients in the conventional group and 58 patients in the Franseen group. There was no significant difference between the two groups in terms of the puncture route or number of needle passes for tissue sampling. Both groups showed high sensitivities for cytology (96% vs. 88%, $p=0.17$) and histology (94% vs. 97%, $p=0.67$), without significance. Immunohistochemistry of histological specimens was performed in 46 of 52 (88.5%) patients in the conventional group and in 56 of 58 (96.6%) in the Franseen group ($p=0.14$). Flow cytometry was performed in all ML cases. A concordant result between ML classification and flow cytometry was obtained in 47 out of 52 patients (90.4%) in the conventional group and 49 out of 58 patients (84.5%) in the Franseen group ($p=0.40$). The remaining five cases in the conventional group and nine cases in the Franseen group were B-cell ML cases (11 diffuse large B-cell lymphoma [DLBCL], two follicular lympho-
### Table 1. Characteristics of patients with lymphadenopathy according to the World Health Organization classifications of malignant lymphoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional group (n=70)</th>
<th>Franseen group (n=76)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71 (26–87)</td>
<td>73 (24–93)</td>
<td>0.25</td>
</tr>
<tr>
<td>Female</td>
<td>35 (50.0)</td>
<td>29 (38.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Size of the lesion</td>
<td>29 (10–83)</td>
<td>34 (12–110)</td>
<td>0.14</td>
</tr>
<tr>
<td>Location of the lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
<td>14 (20.0)</td>
<td>21 (27.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Paraaortic</td>
<td>54 (77.1)</td>
<td>54 (71.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hepatic hilum</td>
<td>2 (2.9)</td>
<td>1 (1.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td></td>
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</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>52 (74.3)</td>
<td>58 (76.3)</td>
<td>0.85</td>
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<tr>
<td>Hodgkin lymphoma</td>
<td>0</td>
<td>3</td>
<td>0.25</td>
</tr>
<tr>
<td>Mature B-cell neoplasms</td>
<td>48</td>
<td>48</td>
<td>0.60</td>
</tr>
<tr>
<td>DLBCL, not otherwise specified</td>
<td>25</td>
<td>26</td>
<td>0.85</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>16</td>
<td>15</td>
<td>0.69</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>1</td>
<td>3</td>
<td>0.62</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>2</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td>0</td>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>1</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>T cell/histiocyte-rich large B-cell lymphoma</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Nodal marginal zone lymphoma</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Matura T-cell neoplasms</td>
<td>4</td>
<td>7</td>
<td>0.54</td>
</tr>
<tr>
<td>PTCL, not otherwise specified</td>
<td>1</td>
<td>3</td>
<td>0.62</td>
</tr>
<tr>
<td>AILT</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>ALC/ALK-negative</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>ATLIL</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Follicular T-cell lymphoma</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Metastasis</td>
<td>3 (4.3)</td>
<td>2 (2.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>Benign</td>
<td>15 (21.4)</td>
<td>16 (21.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>4</td>
<td>9</td>
<td>0.25</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>11</td>
<td>7</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).

DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; PTCL, peripheral T-cell lymphoma; AILT, angioimmunoblastic T-cell lymphoma; ALC/ALK, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma.

ma [FL], and one mucosa-associated lymphoid tissue lymphoma); however, flow cytometry showed T-cell-like expression in these cases.

Cytogenetic assessment using G-banded karyotyping was performed for all ML cases. Specific translocations were found in 35 patients: t(14;18)(q32;q21) in 10 FL and three DLBCL cases in the conventional group, and nine FL and five DLBCL cases in the Franseen group; t(3;14)(q27;q32) in two DLBCL cases in the conventional group and three DLBCL cases in the Franseen group; and t(11;14)(q13;q32) in one mantle case in the Franseen group. Nonspecific and/or complex abnormalities were found in 14 and nine patients in the conventional and Franseen groups, respectively. A normal karyotype was observed in 11 and 13 patients in the conventional and Franseen groups, respectively. Of the remaining 30 patients, cell proliferation was insufficient during cell culture in 13 patients in the convention...
Table 2. Comparison of the lymphadenopathy diagnosis for malignant disease

<table>
<thead>
<tr>
<th></th>
<th>Conventional group (n=70)</th>
<th>Franseen group (n=76)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puncture route</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transesophageal</td>
<td>14 (20.0)</td>
<td>21 (27.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Transgastric</td>
<td>52 (74.3)</td>
<td>48 (63.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Transduodenal</td>
<td>4 (5.7)</td>
<td>7 (9.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>No. of passes</td>
<td>3 (1–6)</td>
<td>4 (1–6)</td>
<td>0.023</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>53/55 (96.4)</td>
<td>53/60 (88.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Specificity</td>
<td>14/15 (93.3)</td>
<td>14/16 (87.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>PPV</td>
<td>53/54 (98.1)</td>
<td>53/55 (96.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>NPV</td>
<td>14/16 (87.5)</td>
<td>14/21 (66.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Accuracy</td>
<td>67/70 (95.7)</td>
<td>67/76 (88.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>52/55 (94.5)</td>
<td>58/60 (96.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Specificity</td>
<td>14/15 (93.3)</td>
<td>16/16 (100.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>PPV</td>
<td>52/53 (98.1)</td>
<td>58/58 (100.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>NPV</td>
<td>14/17 (82.4)</td>
<td>16/18 (88.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Accuracy</td>
<td>66/70 (94.3)</td>
<td>74/76 (97.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>3 (3.9)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (range).

PPV, positive predictive value; NPV, negative predictive value.

Fig. 3. A bleeding case in the Franseen needle group. (A) A 20-mm mediastinum lymphadenopathy (arrow) was detected by computed tomography. (B) The lymphadenopathy was punctured via a transesophageal route using a 19-gauge Franseen needle. (C) Mediastinal enlargement with chest pain was observed one day after puncture test. The vessel (arrowheads) was observed in the hematoma around the lymphadenopathy using contrast computed tomography. (D) Embolization of the vessel was required for hemostasis.
Table 3. A logistic analysis of the relating factors in the accurate diagnosis of lymphadenopathy through cytology or histology

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis (cytology)</th>
<th>Multivariate analysis (cytology)</th>
<th>Univariate analysis (histology)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Franseen group</td>
<td>0.33 (0.09–1.29)</td>
<td>0.11</td>
<td>0.37 (0.10–1.46)</td>
</tr>
<tr>
<td>Age, ≥72 yr</td>
<td>0.69 (0.21–2.29)</td>
<td>0.55</td>
<td>1.00 (0.20–5.13)</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>0.23 (0.05–1.10)</td>
<td>0.07</td>
<td>0.26 (0.05–1.22)</td>
</tr>
<tr>
<td>Tumor size, ≥32 mm</td>
<td>0.71 (0.22–2.36)</td>
<td>0.58</td>
<td>1.22 (0.24–6.27)</td>
</tr>
<tr>
<td>Number of passes, ≥4 times</td>
<td>1.23 (0.38–4.00)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Puncture route (gastric)</td>
<td>1.10 (0.31–3.84)</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Table 4. Subgroup analyses of the lymphadenopathy diagnosis by the puncture route

<table>
<thead>
<tr>
<th>Esophageal</th>
<th>Conventional group</th>
<th>Franseen group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Sensitivity</td>
<td>8/8 (100.0)</td>
<td>9/10 (90.0)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>6/6 (100.0)</td>
<td>10/11 (90.9)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>8/8 (100.0)</td>
<td>9/10 (90.0)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>6/6 (100.0)</td>
<td>10/11 (90.9)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>14/14 (100.0)</td>
<td>19/21 (90.5)</td>
</tr>
<tr>
<td>Histology</td>
<td>Sensitivity</td>
<td>8/8 (100.0)</td>
<td>9/10 (90.0)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>6/6 (100.0)</td>
<td>11/11 (100.0)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>8/8 (100.0)</td>
<td>9/9 (100.0)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>6/6 (100.0)</td>
<td>11/12 (91.7)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>14/14 (100.0)</td>
<td>20/21 (95.2)</td>
</tr>
<tr>
<td>Gastric</td>
<td>Cytology</td>
<td>Sensitivity</td>
<td>43/45 (95.6)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>7/7 (100.0)</td>
<td>3/3 (100.0)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>43/43 (100.0)</td>
<td>39/39 (100.0)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>7/9 (77.8)</td>
<td>3/9 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>50/52 (96.2)</td>
<td>42/48 (87.5)</td>
</tr>
<tr>
<td>Histology</td>
<td>Sensitivity</td>
<td>42/45 (93.3)</td>
<td>44/45 (97.8)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>7/7 (100.0)</td>
<td>3/3 (100.0)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>42/42 (100.0)</td>
<td>44/44 (100.0)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>7/10 (70.0)</td>
<td>3/4 (75.0)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>49/52 (94.2)</td>
<td>47/48 (97.9)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Cytology</td>
<td>Sensitivity</td>
<td>2/2 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>1/2 (50.0)</td>
<td>2/2 (100.0)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>2/3 (66.7)</td>
<td>5/5 (100.0)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>1/1 (100.0)</td>
<td>2/2 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>3/4 (75.0)</td>
<td>7/7 (100.0)</td>
</tr>
<tr>
<td>Histology</td>
<td>Sensitivity</td>
<td>2/2 (100.0)</td>
<td>5/5 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>1/2 (50.0)</td>
<td>2/2 (100.0)</td>
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<tr>
<td></td>
<td>PPV</td>
<td>2/3 (66.7)</td>
<td>5/5 (100.0)</td>
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<tr>
<td></td>
<td>NPV</td>
<td>1/1 (100.0)</td>
<td>2/2 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>3/4 (75.0)</td>
<td>7/7 (100.0)</td>
</tr>
</tbody>
</table>

Values are presented as number/total number (%). PPV, positive predictive value; NPV, negative predictive value.

Table 5. Comparison of the malignant lymphoma diagnoses in the conventional and Franseen groups

<table>
<thead>
<tr>
<th></th>
<th>Conventional group (n=52)</th>
<th>Franseen group (n=58)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puncture route</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transesophageal</td>
<td>5 (9.6)</td>
<td>8 (13.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Transgastric</td>
<td>45 (86.5)</td>
<td>45 (77.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Transduodenal</td>
<td>2 (3.8)</td>
<td>5 (8.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>No. of passes ≥4 times</td>
<td>3 (1–6)</td>
<td>4 (1–6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology</td>
<td>50 (96.2)</td>
<td>51 (87.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Histology</td>
<td>49 (94.2)</td>
<td>56 (96.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>IHC evaluation rate in histological specimen</td>
<td>46 (88.5)</td>
<td>56 (96.6)</td>
<td>0.14</td>
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<tr>
<td>Flow cytometry</td>
<td>47 (90.4)</td>
<td>49 (84.5)</td>
<td>0.40</td>
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<tr>
<td>Cytogenetic assessment</td>
<td>33 (63.5)</td>
<td>45 (77.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diagnostic rate of WHO classifications</td>
<td>48 (92.3)</td>
<td>57 (98.3)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (range). IHC, immunohistochemistry; WHO, World Health Organization.

Okuno et al. 19-G FNA/FNB needles for lymphadenopathy
DISCUSSION

There have been three comparative studies of 22-G or 25-G conventional and Franseen needles for the diagnosis of lymphadenopathy, with the diagnostic accuracy of 22-G or 25-G needles reportedly at 65% to 88%. However, no previous studies have compared 19-G conventional and Franseen needles in cases of lymphadenopathy. The use of a 19-G needle ensured that large amounts of tissue samples were obtained, and the diagnostic accuracy of our study with both 19-G needle types was 94-97%. Therefore, using a 19-G needle ensures that sufficient tissue samples were obtained for the accurate diagnosis of lymphadenopathy. Franseen needles have been reported to be useful for tissue sampling; however, there was no significant difference in the diagnostic accuracy of lymphadenopathy between the two 19-G needle types. The 19-G conventional needle can obtain sufficient tissue samples because of the structure of lymphadenopathy. The pathological findings showed that the lymphadenopathy had high cell density, low fibrous tissue, and weak tissue connection (Fig. 1C). These structures differ from those in pancreatic cancer, suggesting that even conventional needles can be used to collect sufficient tissue. In this study, the median number of needle passes was significantly higher in the Franseen group (four) than in the conventional group (three). This difference was mainly due to the revision of our strategy for obtaining cytogenetic assessment samples. We typically performed two needle passes to obtain pathological specimens and added another needle pass to obtain samples for cytogenetic assessment in the early half-period when the conventional needle was frequently used. However, due to the low sensitivity (14.3%) of the cytogenetic assessment performed in a previous report, we increased the number of needle passes required to collect samples for cytogenetic assessment from one to two in the late half-period; at this time, the Franseen needle was frequently used. Therefore, the increased number of needle passes in the Franseen group may have only affected the sensitivity of the cytogenetic assessment and not pathological sample acquisition.

ML classification is important for determining treatment plans and is based on the results of immunohistochemistry, flow cytometry, and/or cytogenetic assessments. Immunohistochemistry was performed in 92.7% of patients (102/110) using both 19-G needle types. Sufficient histological ML tissue samples could not be obtained in five of the remaining cases, and the other three cases were difficult to evaluate because the samples included a high concentration of necrotic tissues. As both the conventional and Franseen groups showed a high evaluation rate, there was no significant difference in the immunohistochemical evaluation rate (88% vs. 97%, p=0.14). Therefore, the 19-G needle can be used to obtain sufficient tissue samples for immunohistochemistry, regardless of the needle type. Flow cytometry requires smaller tissue sample sizes and can obtain results faster than immunohistochemistry. Notably, this rapid provision of information is particularly important for commencing treatment. The flow cytometry sensitivity was also high in both groups (90% in the conventional group versus 85% in the Franseen group). Previous reports showed high sensitivity (81.0%) of flow cytometry using a 19-G conventional needle; therefore, flow cytometry can be evaluated using a 19-G needle, regardless of the needle type.

Cytogenetic assessment using G-banded karyotyping and/or FISH is also helpful for evaluating ML classifications with genetic abnormalities, such as with t(14;18)(q32;q21) and t(11;14) (q13;q32) translocation. However, this method requires a large number of cells to enable the examination of cells while in metaphase, and the sensitivity of G-banded karyotyping was reported to be only 14.3% using 19-G conventional needle-obtained tissue. In this study, G-band sensitivity in the Franseen group (78%) was higher than in the conventional group (63%). This suggests that the use of the 19-G Franseen needle can improve the sensitivity of cytogenetic assessment; however, the median pass number was larger in the Franseen group (four times) than in the conventional group (three times). Therefore, the results should be evaluated by subtracting the number of needle passes. Finally, 105 (95%) of the 110 patients with ML were diagnosed using a combination of immunohistochemistry, flow cytometry, and/or cytogenetic assessment. There was no significant difference in the rate of ML diagnosis between the conventional (92%) and Franseen groups (98%, p=0.19). This result suggests that 19-G needles have high diagnostic ability for ML classification.

Three cases of bleeding occurred in the Franseen group. Although blood vessels were observed in all cases using the Doppler mode before EUS-FNA, undetectable minor vessels were injured. Benign lymphadenopathies, such as sarcoidosis, involve several minor vessels that can only be detected by contrast-enhanced EUS, and two of the bleeding cases were sarcoidosis. A large-gauge needle can increase the risk of vessel injury; however, the 19-G conventional needle group did not experience any AEs. Although it is difficult to determine the relationship between the Franseen needle and bleeding, the shape
of the three needle tips may increase the risk of a minor vessel injury. Considering that both needle types can achieve an accurate diagnosis of lymphadenopathy and ML classification, the 19-G conventional needle seems to be a safe option for tissue sampling.

This study had some limitations. First, because this was a long-term, single-center, retrospective study, improvements in endoscopy and ultrasound processors could potentially favor the use of EUS-FNA in late-stage cases. However, although most Franseen needle cases were included in the late half-period of the study, there were no significant differences in the pathological findings. This suggests that the use of a conventional needle is sufficient for diagnosing lymphadenopathy and classifying ML. Second, there was no sampling protocol for the two tubes containing the RPMI 1640 medium. Tissue samples obtained from one needle pass were divided into two tubes during the early half-period. However, in the late half-period, the tissue sample obtained after two needle passes was divided into two tubes to improve the tissue volume and sensitivity of the cytogenetic assessment, which also affected the number of needle passes in each group.

In conclusion, both 19-G conventional and Franseen needles showed high accuracy for lymphadenopathy and ML classification. Both needle types ensured sufficient tissue collection and avoidance of AEs; therefore, a 19-G conventional needle can be used for lymphadenopathy diagnosis.

Supplementary Material

**Supplementary Table 1.** Characteristics of patients who underwent 22-G/25-G needle biopsy.

**Supplementary Table 2.** Comparison of the malignant lymphoma diagnoses after 22-G needle biopsy.

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.095.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: MO, KI, TM, TT, AS, YN; Investigation: MO, YI, YK, NW, YS, JK; Methodology: MO, KI, TM, TT, AS, YN; Supervision: SK, TI, ET, MS; Writing—original draft: MO; Writing—review & editing: all authors.

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REFERENCES

7. Sugimoto M, Irie H, Takagi T, et al. Efficacy of EUS-guided FNB using a Franseen needle for tissue acquisition and microsatellite in-


A novel fully covered metal stent for unresectable malignant distal biliary obstruction: results of a multicenter prospective study

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The non-obstruction rate of a novel fully covered metal stent for malignant distal biliary obstructions is comparable to that reported earlier, but shorter than what was expected. The short length of bile duct stenosis is a significant risk factor for stent migration.
INTRODUCTION

Unresectable malignant distal biliary obstruction (MDBO) results in obstructive jaundice that requires biliary drainage not only to improve the quality of life but also to achieve a drainage effect before the induction of chemotherapy. Currently, endoscopic transpapillary biliary drainage is the standard procedure for treating unresectable MDBO. Clinical guidelines recommend self-expandable metal stents (SEMSs) because they have a lower risk of stent dysfunction compared with plastic stents. Recent advances in anticancer treatment have improved the prognosis of patients with unresectable MDBO; therefore, longer stent patency is required.

The selection of covered or uncovered SEMSs for MDBO is debatable. Uncovered SEMSs pose the risk of stent occlusion following tumor ingrowth into the metal mesh. Covered SEMSs have been developed to resolve this problem. However, covered SEMSs are associated with a lower risk of tumor ingrowth, but a higher risk of stent migration. A recent systematic review and meta-analysis comparing the performances of covered and uncovered SEMSs in patients with unresectable MDBO concluded that the data showed no added benefits of covered SEMSs. However, based on the results of randomized controlled trials conducted in Japan, the patency of covered SEMSs is superior to that of uncovered SEMSs, with comparative adverse events. Therefore, covered SEMSs are mainly used in Japan, and covered SEMSs with longer stent patency and fewer stent migrations are strongly needed.

The fully covered SEMS (Cook Evolution Biliary Stent; Cook Ireland Ltd.) used in this study was constructed from a single woven cross-structured nitinol wire with a silicone-covered membrane. These stents have three potential advantages. First, although a low radial force (RF) is considered a risk factor for stent migration, this stent has a relatively high RF, and an appropriate axial force (AF) is expected to reduce stent migration. Secondly, the stent was flanged at both ends to reduce the risk of migration (Fig. 1A). Third, the stent is placed using a controlled-release, trigger-driven delivery system (Fig. 1B). This system allows the SEMS to be recaptured before stent placement, in case repositioning is necessary. This system also makes it possible to deploy the stent in an appropriate position; consequently, it is expected to reduce stent migration.

Therefore, we conducted a single-arm prospective study to determine the clinical efficacy of a novel, fully covered SEMS for treating unresectable MDBO.

METHODS

Study design
This multicenter, single-arm, prospective study was conducted at Kobe University, Japan. The patients were recruited between March 2018 and August 2019 from 12 hospitals in Japan (Kobe University Hospital, Osaka Saiseikai Nakatsu Hospital, Akashi Medical Center, Kita-Harima Medical Center, Kobe Medical Center, Kakogawa Central Hospital, Hyogo Cancer Center, Konan Hospital, Rokko Island Hospital, Takatsuki Hospital, Shisco Municipal Hospital, and Kobe Red Cross Hospital). The inclusion criteria were as follows: (1) age ≥20 years with the ability to provide informed consent and (2) pathologically proven, unresectable MDBO. MDBO was defined as a biliary obstruction.
stricture located 2 cm from the bifurcation. The exclusion criteria were as follows: (1) jaundice or cholangitis that could not be controlled by biliary drainage; (2) severe dysfunction in other organs (American Society of Anesthesiologist physical status grade III or IV); (3) Eastern Cooperative Oncology Group performance status 4; (4) life expectancy of less than 3 months; (5) coexisting hilar biliary stenosis; and (6) surgically altered upper gastrointestinal anatomy, such as Billroth-I, Billroth-II, or Roux-en-Y reconstruction. Patients in whom biliary cannulation by endoscopic retrograde cholangiopancreatography was unsuccessful were excluded from the study. Medical records were reviewed from the date of inclusion in the study until February 2020.

**Procedures**

In all the patients, SEMS placement was performed under conscious sedation by an experienced endoscopist at 12 hospitals. SEMSs were placed after endoscopic sphincterotomy. All SEMSs were 10 mm in diameter, and their lengths (6 and 8 cm) were determined at the discretion of each hospital. The SEMSs covered the biliary stricture, and the lower end was placed across the papilla of Vater. It was unclear whether the patient had been treated with a plastic stent or other biliary drainage procedures prior to SEMS placement.

**Outcomes**

The primary outcome was a non-obstruction rate at 6 months. The secondary outcomes were overall survival (OS), recurrent biliary obstruction (RBO), time to RBO (TRBO), technical and clinical success, and adverse events.

The outcomes were defined according to the TOKYO criteria. RBO was defined as either stent occlusion accompanied by elevated liver enzyme levels and bile duct dilation on any image or symptomatic stent migration. The reason for stent occlusion was determined based on endoscopic or other imaging findings. TRBO was measured from the day of SEMS placement until RBO. TRBO was estimated using the Kaplan-Meier method. In the estimation, patient death and complications other than RBO requiring SEMS removal were treated as censored cases at the time of death and SEMS removal, respectively. Non-obstruction rates at 6 months were also estimated using the Kaplan-Meier method, where the non-obstruction rate is the rate of patients not subjected to RBO at 6 months. Technical success was defined as the successful placement of a SEMS with sufficient coverage of the stricture. Clinical success was defined as a reduction in serum bilirubin less than 1.3 mg/dL, or a decrease of ≥50% within 14 days. Pancreatitis, cholangitis, cholecystitis, perforation, bleeding, and stent migration were evaluated according to the TOKYO criteria. The length of the biliary strictures was measured using fluoroscopy.

**Statistical analysis**

In a previous study, the stent patency probability of a fully covered SEMS for MDBO at 6 months was 64%. Based on the results of this study, we hypothesized that the threshold for the stent non-obstruction rate at 6 months was 75%, and the expected stent patency probability at 6 months was 60%. Under these assumptions, the number of patients needed for this study was estimated to be 80, with a significance level of 0.05, a power of 0.8, and an α error of 0.05. Considering a withdrawal rate of 10%, the planned sample size was set at 90.

All statistical analyses were performed using JMP software version 11 (SAS Institute). All p-values were two-sided. Statistical significance was set at p<0.05. significant. Non-obstruction

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*Fig. 1.* (A) The fully covered self-expandable metal stent (SEMS) used in this study was constructed using a single woven nitinol wire with a silicone-covered membrane. The stent had flanged ends to mitigate migration. (B) The stent was deployed using a controlled-release, trigger-driven delivery system. This system allowed recapturing of the SEMS before complete deployment if repositioning was required.
rates at 6 months, RBO, and OS were evaluated using the Kaplan-Meier analysis. RBOs were compared using log-rank tests. Risk factor analysis of stent migration was performed using the Cox proportional hazards model. Baseline variables ($p<0.05$) in the univariate analysis were included in the multivariate analysis.

**Ethics statements**
This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of each hospital. All the patients provided written informed consent before participating in the study. This trial was registered with the University Hospital Medical Information Network (UMIN) under trial number 000030022.

**RESULTS**

**Patient characteristics**
The study period was repeatedly extended to reach the planned 90 patients; however, this was unsuccessful because of a higher rate of stent migration. According to the study protocol, case recruitment was discontinued upon the agreement of all participating hospitals, and recruitment was terminated in 81 patients. Eight of the 81 patients were excluded after study inclusion (four patients failed to undergo SEMS placement, two patients had coexisting hilar biliary stenosis that was noticed later, one patient had surgically altered anatomy that was noticed later, and one patient withdrew consent), and a total of 73 patients were enrolled in this study. Table 1 shows the baseline patient characteristics. The predominant cause of MDBO was pancreatic cancer (76.7%, 56/73). Prior biliary drainage was performed in 71.2% (52/73) of the cases. Prior cancer treatment, including chemotherapy or radiotherapy, was performed in 30.1% (22/73) of the cases, and cancer treatment after the procedure was performed in 57.5% (42/73) of the cases.

**Technical success, clinical success, RBO, and adverse events**
Table 2 shows the technical and clinical success, RBO, and the

### Table 1. Baselines patient’s characteristics ($n=73$)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>$72 (44–93)$</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>$35 (47.9)$</td>
</tr>
<tr>
<td>Female</td>
<td>$38 (52.1)$</td>
</tr>
<tr>
<td>Cause of MDBO</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>$56 (76.7)$</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>$14 (19.2)$</td>
</tr>
<tr>
<td>Others</td>
<td>$3 (4.1)$</td>
</tr>
<tr>
<td>Clinical stage (UICC 8th)</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>$46 (63.0)$</td>
</tr>
<tr>
<td>Stage III</td>
<td>$16 (21.9)$</td>
</tr>
<tr>
<td>Others</td>
<td>$11 (15.1)$</td>
</tr>
<tr>
<td>Prior drainage</td>
<td></td>
</tr>
<tr>
<td>Endoscopic plastic stent placement</td>
<td>$52 (71.2)$</td>
</tr>
<tr>
<td>Endoscopic nasobiliary drainage</td>
<td>$6 (8.2)$</td>
</tr>
<tr>
<td>Percutaneous transhepatic biliary drainage</td>
<td>$1 (1.4)$</td>
</tr>
<tr>
<td>None</td>
<td>$14 (19.2)$</td>
</tr>
<tr>
<td>Prior cancer treatment</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy/radiotherapy</td>
<td>$22 (30.1)$</td>
</tr>
<tr>
<td>None</td>
<td>$51 (69.9)$</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>$23 (31.5)$</td>
</tr>
<tr>
<td>1</td>
<td>$38 (52.1)$</td>
</tr>
<tr>
<td>2</td>
<td>$9 (12.3)$</td>
</tr>
<tr>
<td>3</td>
<td>$3 (4.1)$</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>$1.4 (0.1–11.6)$</td>
</tr>
<tr>
<td>WBC ($\times 10^3$/μL)</td>
<td>$5,800 (1,560–14,570)$</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>$0.98 (0.01–19.23)$</td>
</tr>
<tr>
<td>Stricture length (cm)</td>
<td>$3 (1–6)$</td>
</tr>
<tr>
<td>Stent length</td>
<td></td>
</tr>
<tr>
<td>6 cm</td>
<td>$40 (54.8)$</td>
</tr>
<tr>
<td>8 cm</td>
<td>$33 (45.2)$</td>
</tr>
<tr>
<td>Cancer treatment after procedure</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy/radiotherapy</td>
<td>$42 (57.5)$</td>
</tr>
<tr>
<td>None</td>
<td>$31 (42.5)$</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).

MDBO, malignant distal biliary obstruction; UICC, Union for International Cancer Control; WBC, white blood cell; CRP, C-reactive protein.

### Table 2. Clinical outcomes ($n=73$)

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical success</td>
<td>$73 (100.0)$</td>
</tr>
<tr>
<td>Clinical success</td>
<td>$71 (97.3)$</td>
</tr>
<tr>
<td>Recurrent biliary obstruction</td>
<td>$36 (49.3)$</td>
</tr>
<tr>
<td>Distal migration</td>
<td>$21 (28.8)$</td>
</tr>
<tr>
<td>Proximal migration</td>
<td>$5 (6.8)$</td>
</tr>
<tr>
<td>Sludge</td>
<td>$5 (6.8)$</td>
</tr>
<tr>
<td>Overgrowth</td>
<td>$2 (2.7)$</td>
</tr>
<tr>
<td>Others</td>
<td>$3 (4.1)$</td>
</tr>
<tr>
<td>Adverse events</td>
<td>$15 (20.5)$a</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>$7 (9.6)$</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>$6 (8.2)$</td>
</tr>
<tr>
<td>Non-occlusive cholangitis</td>
<td>$4 (5.5)$</td>
</tr>
<tr>
<td>Median observational period (day)</td>
<td>$217 (110–371)$</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range).

aOne patient had three adverse events.
occurrence of adverse events. Technical success was achieved in 100% (73/73) of the cases. Clinical success was achieved in 97.3% (71/73) of patients. RBO occurred in 49.3% (36/73) of cases, and the causes of RBO were distal migration in 28.8% (21/73), proximal migration in 6.8% (5/73), sludge obstruction in 6.8% (5/73), overgrowth in 2.7% (2/73), and others in 4.1% (3/73). Adverse events occurred in 20.5% (15/73) of the cases, pancreatitis in 9.6% (7/73), cholecystitis in 8.2% (6/73), and non-occlusive cholangitis in 5.5% (4/73). No adverse events resulted in death. The median observational period was 217 days (interquartile range, 110–371 days).

Patient survival, time to stent patency, and TRBO
Figure 2 shows the Kaplan-Meier curves for patient survival and TRBO. The median OS was 233 days. The median TRBO score was 216. The non-obstruction rate at 6 months was 61%.

Risk factors for stent migration
The non-obstruction rate at 6 months was lower than expected, which could be due to the high frequency of stent migration. Therefore, we analyzed the risk factors for stent migration. Table 3 shows the results of univariate and multivariate analyses using the Cox proportional hazards model, using which the risk factors related to stent migration were investigated. The cutoff

Table 3. Risk factor analysis for stent migration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>38/35</td>
<td>1.83 (0.83–4.33)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44–93</td>
<td></td>
<td>1.01 (0.96–1.02)</td>
</tr>
<tr>
<td>Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others/pancreatic cancer</td>
<td>17/56</td>
<td>1.33 (0.51–3.09)</td>
</tr>
<tr>
<td>Prior drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/yes</td>
<td>14/59</td>
<td>1.12 (0.37–2.81)</td>
</tr>
<tr>
<td>Prior cancer treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>22/51</td>
<td>3.19 (1.10–13.50)</td>
</tr>
<tr>
<td>Stenosis &lt;2.2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>3.00 (1.36–7.06)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Stent length (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/6</td>
<td>33/40</td>
<td>1.53 (0.68–3.64)</td>
</tr>
<tr>
<td>Cancer treatment after procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/yes</td>
<td>31/42</td>
<td>1.16 (0.51–2.84)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
*A p-value less than 0.05 was considered statistically significant.
value for the length of bile stenosis was calculated using a receiver operating characteristic curve. Significant risk factors for stent migration in univariate analysis were the prior cancer treatment to procedure (hazard ratio [HR] 3.19; 95% confidence interval [CI], 1.10–13.50; \( p = 0.03 \)) and the length of bile duct stenosis <2.2 cm (HR, 3.00; 95% CI, 1.36–7.06; \( p = 0.006 \)). Multivariate analysis revealed that the length of bile duct stenosis <2.2 cm was the only significant risk factor for stent migration (HR, 2.58; 95% CI, 1.16–6.14; \( p = 0.02 \)).

When the analysis was limited to patients with a length of bile duct stenosis of 2.2 cm or more, RBO occurred in 39.5% (17/43) of cases, and the cause of RBO was distal migration in 14.0% (6/43) of cases, proximal migration in 9.3% (4/43), sludge obstruction in 7.0% (3/43), overgrowth in 2.3% (1/43), and others in 7.0% (3/43). Compared to the group with bile duct stenosis <2.2 cm, no significant differences were observed in stent length, prior drainage, prior cancer therapy, cancer treatment after the procedure, or cancer stage; in contrast, the migration rate was significantly lower (10/43 [23.3%] vs. 16/30 [53.3%], \( p = 0.004 \)) (Table 4). The median TRBO of the patients with a length of bile duct stenosis of 2.2 cm or more and others was 276 days (Fig. 3A) and 158 days (Fig. 3B), respectively. The non-obstruction rate at 6 months of patients with a length of bile duct stenosis of 2.2 cm or more and others was 68% (Fig. 3A) and 55% (Fig. 3B), respectively. Although not statistically significant, patients with bile duct stenosis of 2.2 cm or more

<table>
<thead>
<tr>
<th>The length of bile duct stenosis</th>
<th>&lt;2.2 cm (n=30)</th>
<th>&gt;2.2 cm (n=43)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent length 6 mm</td>
<td>15 (50.0)</td>
<td>25 (58.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Prior drainage</td>
<td>22 (73.3)</td>
<td>37 (86.0)</td>
<td>0.17</td>
</tr>
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<td>Prior cancer therapy</td>
<td>6 (20.0)</td>
<td>16 (37.2)</td>
<td>0.11</td>
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<tr>
<td>Cancer treatment after procedure</td>
<td>18 (60.0)</td>
<td>24 (55.8)</td>
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<tr>
<td>Migration</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stage (1/2/3/4)</td>
<td>1 (3.3)/2 (6.7)/8 (26.7)/19 (63.3)</td>
<td>2 (4.7)/6 (14.0)/9 (20.9)/26 (60.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Fig. 3. The Kaplan–Meier curve shows the time to recurrent biliary obstruction (TRBO) of the patients with a length of bile duct stenosis of 2.2 cm or more (A) and others (B). The median TRBO was 276 days (A) and 158 days (B). Although not statistically significant, patients with a length of bile duct stenosis of 2.2 cm or more tended to have a longer TRBO than others (\( p = 0.068 \)).
tended to have longer TRBO than others ($p=0.068$).

**Reintervention**

Reintervention was performed in 35 (47.9%) patients. The reasons for reintervention were RBO ($n=33$) and cholecystitis ($n=2$). Reintervention was successful in all cases. The procedure types for reintervention were uncovered SEMS placement ($n=15$), covered SEMS placement ($n=11$), plastic stent placement ($n=7$), and endoscopic sludge removal ($n=2$). SEMS removal was successful in 10 of 11 patients (90.9%). In one case of SEMS removal, duodenal perforation caused by the endoscope occurred but was successfully treated with endoscopic clipping. The median time to reintervention was 91 days (range, 6-385 days).

**DISCUSSION**

This study investigated the clinical performance of a novel, fully covered SEMS for treating unresectable MDBO. The results showed that the non-obstruction rate at 6 months was comparable to that reported earlier, but the results were not satisfactory. The high frequency of stent migration is thought to be the reason for inadequate stent patency. The length of bile duct stenosis <2.2 cm was the only significant risk factor for stent migration.

Recent progress in chemotherapy for unresectable malignant tumors is remarkable. Biliary drainage for MDBO is important not only for improving quality of life but also for prognostic purposes. Endoscopic biliary drainage is a widely accepted standard treatment for MDBO. The superiority of SEMSs over plastic stents for unresectable MDBO has been reported in many studies and their evaluation has already been established. Whether covered or uncovered SEMSs are superior remains unclear. The results of the present study are comparable with those of a recent systematic review. However, a recent study reported the results of fully covered SEMSs showing long TRBO with low migration rates. Yamao et al. reported a TRBO of 536 days, RBO of 14%, and migration of 4% for fully covered SEMS in the treatment of MDBO, whereas Marui et al. reported a TRBO of 445 days, RBO of 15%, and migration of 4%. With the recent emergence of covered SEMSs with longer TRBO, large-scale comparative studies are needed to clarify the superiority of novel covered SEMSs over uncovered SEMSs.

Stent migration is a common adverse event encountered in covered SEMSs. However, few studies have reported the risk factors for migration. Nakai et al. investigated risk factors for stent migration in patients with unresectable pancreatic cancer who underwent covered SEMS placement for MDBO. Covered SEMSs with a low RF, duodenal invasion, and chemotherapy have been reported as risk factors for stent migration. In the present study, stricture length (2 cm) was not found to be a significant risk factor for migration. However, stent migration is common in cases of ampullary cancer and is thought to be due to short stenosis. To our knowledge, our study is the first to report that bile duct stenosis of <2.2 cm is a risk factor for stent migration. Based on this finding, a fully covered SEMS should be avoided in patients with MDBO and short stenosis lengths.

The results of this study showed that the novel, fully covered SEMS migrated at a high frequency. This may have been due to the mechanical properties of the stents. Isayama et al. speculated that SEMS with high AF might not fit and stay well in the bile duct, thus causing migration. Although the RF and AF of this stent have not yet been investigated, a high AF may cause migration (Supplementary Fig. 1). Further investigation of the mechanical properties of these stents is required. However, the reported advantages of fully covered SEMSs are that ingrowth is less likely to occur and the stent can be easily removed by reintervention. The results of the current study are comparable with those of previous studies.

This study has several limitations. A major limitation is a single-arm design with a small sample size. Another limitation is that the clinical performance of this novel stent is comparable to that of pre-existing stents, but does not provide the expected clinical benefit. The strength of this study was the multicenter prospective design. Further, this is the first report to show that bile duct stenosis of <2.2 cm is a risk factor for stent migration.

In summary, the non-obstruction rate of a novel fully covered biliary SEMS for MDBO is comparable to that reported earlier but shorter than expected. The length of bile duct stenosis (<2.2 cm) was the only significant risk factor for stent migration.

**Supplementary Material**

**Supplementary Fig. 1.** A patient with stage 4 pancreatic cancer. A fully covered self-expandable metal stent was placed (A). One day later, an abdominal X-ray showed that the stent was almost fully dilated and was straightened to change the shape of the bile duct (B). Six months later, the stent was migrated distally. Another patient with stage 4 pancreatic cancer received a woven hook and cross-structured fully covered self-expandable metal stent.
One day later, an abdominal radiograph showed slight dilation of the stent but less change in the shape of the bile duct (D). Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.035.

Conflicts of Interest
The authors have no potential conflicts of interest.

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Author Contributions
Conceptualization: AS, AM; Data curation: AS, TE, KF, TI, SY, YO, KY, IM, SKa, YY, DS, SKo; Formal analysis: AS, YK; Project administration: AS, AM, TK, HS; Supervision: YK; Writing–original draft: AS; Writing–review & editing: all authors.

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REFERENCES


Clinical utility of endoscopic ultrasound-guided tissue acquisition for comprehensive genomic profiling of patients with biliary tract cancer, especially with intrahepatic cholangiocarcinoma

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Clinical utility of endoscopic ultrasound-guided tissue acquisition for comprehensive genomic profiling of patients with biliary tract cancer, especially with intrahepatic cholangiocarcinoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>EUS-TA samples (n=51)</th>
</tr>
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<tbody>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>21</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>18</td>
</tr>
<tr>
<td>Gallbladder neuroendocrine carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Extrahepatic cholangiocarcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Papilla neuroendocrine carcinoma</td>
<td>1</td>
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<tr>
<td>Papilla adenosarcoma</td>
<td>3</td>
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<td>Bile duct neuroendocrine tumor</td>
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<td>Genomic panel test</td>
<td></td>
</tr>
<tr>
<td>Foundation One CDx</td>
<td>15</td>
</tr>
<tr>
<td>OncoGuide NCC Oncopanel System</td>
<td>21</td>
</tr>
<tr>
<td>MSK-IMPACT</td>
<td>3</td>
</tr>
</tbody>
</table>

Factors | Adequacy % (n/N) | Univariate p-value |
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Needle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22-G or 19-G FNB</td>
<td>86 (36/42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Others</td>
<td>33 (3/9)</td>
<td></td>
</tr>
<tr>
<td><strong>Target 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary lesion</td>
<td>88 (29/33)</td>
<td>0.015</td>
</tr>
<tr>
<td>Metastasis</td>
<td>56 (10/18)</td>
<td></td>
</tr>
<tr>
<td><strong>Target 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver lesion</td>
<td>84 (27/32)</td>
<td>0.10</td>
</tr>
<tr>
<td>Others</td>
<td>63 (12/19)</td>
<td></td>
</tr>
<tr>
<td><strong>Target size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 mm</td>
<td>100 (30/30)</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;30 mm</td>
<td>43 (9/21)</td>
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</tr>
<tr>
<td><strong>No. of punctures</strong></td>
<td></td>
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<tr>
<td>≥3 times</td>
<td>90 (27/30)</td>
<td>0.016</td>
</tr>
<tr>
<td>&lt;3 times</td>
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<tr>
<td><strong>Puncture route</strong></td>
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<tr>
<td>Transgastric</td>
<td>68 (15/22)</td>
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</tr>
<tr>
<td>Transduodenal</td>
<td>83 (24/29)</td>
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</table>

Using 22-G or larger FNB-needle vs. Surgical specimens

86% vs. 94%
p=0.45

Using 22-G FNB-needle for the patient with intrahepatic cholangiocarcinoma

⇒ OncoGuide NCC Oncopanel System

22-G or larger FNB-needle, target of primary lesion, target size (≥30 mm) and number of punctures (≥3 times) were significant factors associated with sample’s adequacy.
INTRODUCTION

Biliary tract cancer (BTC) is the sixth leading cause of cancer mortality and approximately 17,000 people with BTC die annually in Japan. According to data from 2009 to 2011 in Japan, the five-year survival rate is 24.5%. Although surgical resection is the only curative therapy, half of the BTC cases are unresectable at the time of diagnosis. According to the results from the Japanese Biliary Tract Cancer Statistics Registry from 1998 to 2004, the curative resection rate was 47.3% (752/1,590) in patients with gallbladder cancer (GBC) and 46.7% (884/1,894) in those with bile duct cancer. Hence, chemotherapy is the standard therapy for BTCs.

The first-line chemotherapy is a cisplatin-gemcitabine-based treatment, yielding a median overall survival period of 11.7 months in a cisplatin-gemcitabine group (ABC-02 trial), 13.5 months in a cisplatin-gemcitabine plus tegafur/gimeracil/oteracil group (KHBO1401-MITSUBA trial), and 16.8 months in a cisplatin-gemcitabine plus durvalumab group.

Combination chemotherapy of 5-fluorouracil and oxaliplatin, and liposomal irinotecan in combination with fluorouracil and leucovorin, have been recommended in the National Comprehensive Cancer Network (NCCN) guidelines as second-line chemotherapy after the failure of cisplatin-gemcitabine chemotherapy. However, as no evidence-based second-line chemotherapy is currently recommended for BTC, the gemcitabine plus cisplatin-based treatment is, in effect, also its last-line treatment. The small array of chemotherapies available for BTC contributes to its poor prognosis; therefore, alternative therapeutic drugs are urgently required.

The NCCN guidelines recommend that molecular analysis be performed when a patient is first diagnosed with unresectable BTC. Comprehensive genomic profiling (CGP) has been approved in Japan since June 2019, and nearly 38.9% (93/239) of Japanese patients with BTCs in one study harbored genetic variants that were potential therapeutic targets. Certain targeted molecular therapies, such as pemigatinib for fibroblast growth factor receptor 2 (FGFR2) fusions and ivosidenib for isocitrate dehydrogenase-1 (IDH1) mutations, have been granted accelerated approval by the United States Food and Drug Administration, and pemigatinib has been approved in Japan since June 2021. Thus, precision medicine has been spreading not only in medical research but also in clinical practice.

Endoscopic ultrasound-guided tissue acquisition (EUS-TA) has been useful for BTC, and a previous meta-analysis involving 957 patients with BTC demonstrated that the sensitivity and specificity of EUS-TA were 80% (95% confidence interval [CI], 74%–86%) and 97% (95% CI, 94%–99%), respectively. EUS-TA has already been used to obtain tissue samples for CGP, for example, in patients with pancreatic cancers. However, to the best of our knowledge, there are no reports describing the best method for obtaining CGP samples from patients with BTC. Therefore, we conducted this study with the aim of evaluating the utility of EUS-TA for CGP in a clinical setting and determining the factors associated with the adequacy of CGP in patients with BTC.
METHODS

Population
Tissue samples were obtained for tissue-based CGP analysis at the Aichi Cancer Center Hospital, Japan, from October 2019 to December 2022. Demographic and clinical information of all patients were retrospectively collected from the Aichi Cancer Center Hospital Clinical Database.

Endoscopic procedure
All EUS-TA procedures were performed using linear array endoscopes (Olympus GF-UCT260, Olympus Medical Systems or EG-580UT or GF-740UT, Fujifilm). We used EZ Shot 3 Plus needles (Olympus Medical Systems) for fine-needle aspiration (FNA) and Acquire needles (Boston Scientific) for fine-needle biopsy (FNB). We routinely performed three punctures per patient and used rapid on-site evaluation to verify the viability of the tumor tissue and prevent contamination with interstitial, necrotic, or connective tissues. However, we adjusted the number of times by visually examining the white specimens of the samples taken. Each tissue sample was stored in a 10% formalin solution.

Pathological evaluation
At the Aichi Cancer Center Hospital, pathologists evaluated the tumor volume and cellularity of each sample by microscopic examination to determine their appropriateness for CGP analysis. We performed three genomic panel tests using the following: FoundationOne CDx (Foundation Medicine), OncoGuide NCC Oncopanel System (Sysmex Corporation), and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT; Memorial Sloan Kettering Cancer Center).

1) Test criteria
(1) Foundation One CDx
If the total tumor surface area was ≥25 mm$^2$ (5×5 mm), it was divided into (1) one formalin-fixed paraffin-embedded block and one hematoxylin and eosin (H&E)-stained slide or (2) 10 unstained slides (positively-charged and unbaked, 4–5 μm thick) and one H&E-stained slide. If the tumor surface area was <25 mm$^2$, it was divided into 10 unstained slides (4–5 μm thick) to achieve a tissue volume of 1 mm$^3$. Samples were only used if they had ≥20% tumor nuclei content (total number of tumor cells divided by number of cells with nuclei), although ≥30% is optimal.

(2) OncoGuide NCC Oncopanel System
Samples had to meet three criteria: (1) five unstained slides (10 μm thick) could be made; (2) total tumor surface area was ≥16 mm$^2$ (4×4 mm), and (3) percent tumor nuclei content was ≥20%.

(3) MSK-IMPACT
Samples had to meet three criteria: (1) 20 unstained slides (4-5 μm) could be made; (2) total tumor surface area was ≥25 mm$^2$ (5×5 mm), and (3) percent tumor nuclei content was ≥10%.

In this study, samples with <20% tumor nuclei content, insufficient material, or unanalyzable DNA were considered inadequate. Samples for which CGP was successfully performed were considered adequate.

If the tissue criteria were met, MSK-IMPACT panel tests were performed according to the patient’s wishes because MSK-IMPACT panel tests are not covered by insurance in Japan. The Foundation One CDx panel test can detect a large number of genetic alterations compared to the OncoGuide NCC Oncopanel tests. If the samples met the relevant criteria, Foundation One CDx panel tests were performed.

Statistical analyses
We used the chi-square test or Fisher’s exact test to compare categorical variables, with two-sided p-values <0.05 considered as statistically significant. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to determine the optimal target size for CGP. All statistical analyses were performed using Microsoft Excel 2017 (Microsoft Corporation).

Endpoints
The primary endpoint was sample adequacy for CGP. The secondary endpoints were the results of the CGP analysis and the occurrence of adverse events, which were graded according to the lexicon of the American Society for Gastrointestinal Endoscopy.$^{10}$

Ethical statements
Informed consent was obtained from all patients, and the Aichi Cancer Center Hospital Institutional Review Board approved this study (approval number: 2022-0-100).
RESULTS

Patient characteristics
We collected 137 samples from 126 patients for prescreening (Fig. 1). The pathologists judged 113 samples as meeting the suitability criteria and 24 as inadequate. We further excluded 32 samples for which tissue-based CGP was not performed, even though they met the criteria. The remaining 81 samples (81 patients) were considered adequate. We investigated 81 adequate and 24 inadequate samples obtained from 94 patients, the characteristics of whom are summarized in Table 1. The median age of the patients was 65 years, and 46 of 94 patients were women. The primary tumors were intrahepatic cholangiocarcinoma (ICC) (n=37), extrahepatic cholangiocarcinoma (ECC) (n=17), GBC (n=34), gallbladder neuroendocrine carcinoma (n=2), papillary neuroendocrine carcinoma (n=2), papillary adenocarcinoma (n=1), and bile duct neuroendocrine tumor (n=1).

In this study, we obtained tissue samples from six patients with ECC using EUS-TA, and punctured the thick bile duct wall (n=4) and the liver invasion area (n=2).

CGP was performed most frequently using the Foundation One CDx panel (n=41), followed by the OncoGuide NCC Oncopanel System (n=36) and the MSK-IMPACT panel (n=4).

In seven cases, prescreening was performed twice or thrice, and 18 samples were obtained from these seven patients (Table 1).

Sample adequacy
Table 2 summarizes the sample adequacy for CGP for each sampling method. Overall, 77.1% (81/105) of the samples were adequate for CGP. The sample adequacy of the surgical specimens was 93.8% (30/32), and that of the specimens acquired by EUS-TA and percutaneous liver biopsy were 76.5% (39/51) and 64.7% (11/17), respectively.

Table 3 summarizes the sample adequacy of specimens obtained via EUS-TA, with comparisons based on various factors, including gauge (19-G, 22-G, and 25-G), needle type (FNB

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient (n=94)</th>
<th>Sample (n=105)</th>
<th>EUS-TA sample (n=51)</th>
<th>Surgical sample (n=32)</th>
<th>Percutaneous liver biopsy sample (n=17)</th>
<th>Other samples (n=5)*</th>
</tr>
</thead>
<tbody>
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<td>Sex (female/male)</td>
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<tr>
<td>Diagnosis</td>
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<td>3</td>
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<td>0</td>
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<td>3</td>
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<td>0</td>
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<td>Papilla adenocarcinoma</td>
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<tr>
<td>Foundation One CDx</td>
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<td>41</td>
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<td>OncoGuide NCC Oncopanel System</td>
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</tbody>
</table>

Values are presented as median (range) or number only.

EUS-TA, endoscopic ultrasound-guided tissue acquisition; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets.

*Other samples: skin biopsy (2), bronchoscopic biopsy (1), endoscopic biopsy (1), computed tomography guided biopsy (1).
or FNA), targets (liver lesions or not, primary or metastasis), target size (≥30 mm or <30 mm), number of punctures (≥3 or <3 times), and puncture route (transgastric or transduodenal). Accordingly, needle gauge (19-G vs. 22-G vs. 25-G: 93% vs. 60% vs. 0%, \(p=0.013\)) and type (FNB vs. FNA: 84% vs. 38%, \(p=0.013\)) were associated with sample adequacy. The adequacy rate of samples obtained using 19-G or 22-G (≥22-G) FNB needles was 85.7% (36/42), which was higher than that of the samples obtained using other needles (33%, \(p<0.001\)). The adequacy rate did not differ between samples obtained with ≥22-G FNB needles and surgical specimens (86% vs. 94%, \(p=0.45\)).

Other univariate analyses revealed that the primary lesion (primary vs. metastasis: 88% vs. 56%, \(p=0.015\)), target size (≥30 mm vs. <30 mm: 100% vs. 43%, \(p<0.001\)), and number of punctures (≥3 times vs. <3 times: 90% vs. 57%, \(p=0.016\)) were associated with sample adequacy, whereas liver lesions (liver vs. others: 84% vs. 63%, \(p=0.10\)) and puncture route (transgastric vs. transduodenal: 68% vs. 83%, \(p=0.32\)) were not. We analyzed the ROC curve and defined 30 mm as the cut-off index for the target size (AUC=0.86, \(p<0.001\)). The largest target size was 95 mm, and the lesion was the liver invasion area of the GBC.

A multivariate analysis was not performed because the number of samples obtained using EUS-TA was limited.

In the group in whom 19-G FNB needles were used, 44.8% (13/29) of the samples met the suitability criteria for the Foundation One CDx panel and 6.9% (2/29) met the criteria for the MSK-IMPACT panel. 19-G FNB was available to perform Foundation One CDx more than the other needles (19-G FNB vs. 22-G FNB vs. others: 45% vs. 15% vs. 0%, \(p=0.016\)). Genomic panel tests requiring a larger amount of tumor tissue, such as the Foundation One CDx or MSK-IMPACT panels, were more challenging to perform (Table 4).

### Complications of EUS-TA

Three patients (6%) experienced complications: one had mild abdominal pain (19-G FNB, ICC, liver lesion), one had mild cholangitis (19-G FNB, GBC, gallbladder wall), and one had mild pancreatitis (22-G FNA, ICC, liver lesion). No moderate, severe, or fatal complications were observed. No differences in

#### Table 2. Sample adequacy

<table>
<thead>
<tr>
<th>Sample</th>
<th>Adequacy (%, n/total n)</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>77 (81/105)</td>
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<tr>
<td>EUS-TA</td>
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<tr>
<td>No. of punctures</td>
<td>76 (39/51)</td>
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<tr>
<td>Median (range)</td>
<td>3 (1–6)</td>
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<td>Target size (mm, median [range])</td>
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<tr>
<td>Liver</td>
<td>84.4 (27/32)</td>
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<tr>
<td>Lymph node</td>
<td>55.6 (5/9)</td>
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<tr>
<td>Gallbladder</td>
<td>100.0 (4/4)</td>
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<tr>
<td>Bile duct</td>
<td>50.0 (2/4)</td>
</tr>
<tr>
<td>Pancreatic metastasis</td>
<td>50.0 (1/2)</td>
</tr>
<tr>
<td>Needle gauge</td>
<td></td>
</tr>
<tr>
<td>19-G</td>
<td>93.1 (27/29)</td>
</tr>
<tr>
<td>22-G</td>
<td>60.0 (12/20)</td>
</tr>
<tr>
<td>25-G</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>Needle type</td>
<td></td>
</tr>
<tr>
<td>FNA</td>
<td>37.5 (3/8)</td>
</tr>
<tr>
<td>FNB</td>
<td>83.7 (36/43)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Percutaneous liver biopsy</td>
<td>64.7 (11/17)</td>
</tr>
<tr>
<td>Surgical specimens</td>
<td>93.8 (30/32)</td>
</tr>
</tbody>
</table>

EUS-TA, endoscopic ultrasound-guided tissue acquisition; FNA, fine needle aspiration; FNB, fine needle biopsy.

*Others: skin biopsy (2), bronchoscopic biopsy (1), endoscopic biopsy (1), computed tomography guided biopsy (1).*

#### Table 3. Factors associated with samples adequacy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adequacy (%, n/total n)</th>
<th>Univariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle gauge</td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>19-G</td>
<td>93.1 (27/29)</td>
<td></td>
</tr>
<tr>
<td>22-G</td>
<td>54.5 (12/22)</td>
<td></td>
</tr>
<tr>
<td>25-G</td>
<td>0 (0/2)</td>
<td></td>
</tr>
<tr>
<td>Needle type</td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>FNA</td>
<td>37.5 (3/8)</td>
<td></td>
</tr>
<tr>
<td>FNB</td>
<td>83.7 (36/43)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>22-G+19-G FNB</td>
<td>85.7 (36/42)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>33.3 (3/9)</td>
<td></td>
</tr>
<tr>
<td>Target 1</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Primary lesion</td>
<td>87.9 (29/33)</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>55.6 (10/18)</td>
<td></td>
</tr>
<tr>
<td>Target 2</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Liver lesion</td>
<td>84.4 (27/32)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>63.2 (12/19)</td>
<td></td>
</tr>
<tr>
<td>Target size (mm)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥30</td>
<td>100.0 (30/30)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>42.9 (9/21)</td>
<td></td>
</tr>
<tr>
<td>No. of punctures (time)</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>≥3</td>
<td>90.0 (27/30)</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>57.1 (12/21)</td>
<td></td>
</tr>
<tr>
<td>Puncture route</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Transgastric</td>
<td>68.2 (15/22)</td>
<td></td>
</tr>
<tr>
<td>Transduodenal</td>
<td>82.8 (24/29)</td>
<td></td>
</tr>
</tbody>
</table>

FNA, fine needle aspiration; FNB, fine needle biopsy.

or FNA), targets (liver lesions or not, primary or metastasis), target size (≥30 mm or <30 mm), number of punctures (≥3 or <3 times), and puncture route (transgastric or transduodenal).

Accordingly, needle gauge (19-G vs. 22-G vs. 25-G: 93% vs. 60% vs. 0%, \(p=0.013\)) and type (FNB vs. FNA: 84% vs. 38%, \(p=0.013\)) were associated with sample adequacy. The adequacy rate of samples obtained using 19-G or 22-G (≥22-G) FNB needles was 85.7% (36/42), which was higher than that of the samples obtained using other needles (33%, \(p<0.001\)). The adequacy rate did not differ between samples obtained with ≥22-G FNB needles and surgical specimens (86% vs. 94%, \(p=0.45\)).

Other univariate analyses revealed that the primary lesion (primary vs. metastasis: 88% vs. 56%, \(p=0.015\)), target size (≥30 mm vs. <30 mm: 100% vs. 43%, \(p<0.001\)), and number of punctures (≥3 times vs. <3 times: 90% vs. 57%, \(p=0.016\)) were associated with sample adequacy, whereas liver lesions (liver vs. others: 84% vs. 63%, \(p=0.10\)) and puncture route (transgastric vs. transduodenal: 68% vs. 83%, \(p=0.32\)) were not. We analyzed the ROC curve and defined 30 mm as the cut-off index for the target size (AUC=0.86, \(p<0.001\)). The largest target size was 95 mm, and the lesion was the liver invasion area of the GBC.

A multivariate analysis was not performed because the number of samples obtained using EUS-TA was limited.

In the group in whom 19-G FNB needles were used, 44.8% (13/29) of the samples met the suitability criteria for the Foundation One CDx panel and 6.9% (2/29) met the criteria for the MSK-IMPACT panel. 19-G FNB was available to perform Foundation One CDx more than the other needles (19-G FNB vs. 22-G FNB vs. others: 45% vs. 15% vs. 0%, \(p=0.016\)). Genomic panel tests requiring a larger amount of tumor tissue, such as the Foundation One CDx or MSK-IMPACT panels, were more challenging to perform (Table 4).

#### Complications of EUS-TA

Three patients (6%) experienced complications: one had mild abdominal pain (19-G FNB, ICC, liver lesion), one had mild cholangitis (19-G FNB, GBC, gallbladder wall), and one had mild pancreatitis (22-G FNA, ICC, liver lesion). No moderate, severe, or fatal complications were observed. No differences in
Table 4. EUS-TA and genomic panel tests

<table>
<thead>
<tr>
<th>Genomic panel test</th>
<th>19-G FNB (n=29)</th>
<th>22-G FNB (n=13)</th>
<th>Others (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation One CDx</td>
<td>13 (44.8)</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0.016</td>
</tr>
<tr>
<td>MSK-IMPACT</td>
<td>2 (6.9)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0.71</td>
</tr>
<tr>
<td>OncoGuide NCC</td>
<td>12 (41.4)</td>
<td>6 (46.2)</td>
<td>3 (33.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Inadequate</td>
<td>2 (6.9)</td>
<td>4 (30.8)</td>
<td>6 (66.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

EUS-TA, endoscopic ultrasound-guided tissue acquisition; FNB, fine needle biopsy; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets.

the complication rates were observed according to needle gauge (19-G vs. 22-G vs. 25-G: 7% vs. 5% vs. 0%, p>0.99) or type (FNA vs. FNB: 13% vs. 5%, p=0.41).

CGP results

The CGP results are illustrated in Figure 2. Based on the NCCN guidelines, we identified eight therapeutic molecular markers: IDH1 mutations, FGFR2 fusions, neurotrophic receptor tyrosine kinase fusions, BRAF V600E mutation, receptor tyrosine-protein kinase erbB-2 (ERBB2) amplification, rearrangement during transfection fusions, microsatellite instability-high status, and tumor mutational burden-high status.

The incidence of IDH1 mutations was 9.7% (3/31) among patients with ICC and 0% in patients with ECC or GBC. FGFR2 fusions were detected only in patients with ICC, at a rate of 12.9% (4/31). ERBB2 amplification was detected in 21.4% (6/28) of patients with GBC. Any of the aforementioned targeted therapeutic molecular markers were detected in 22.6% (7/31) of patients with ICC and in 32.1% (9/28) of those with GBC, but in none of the patients with ECC (Table 5).

Kirsten rat sarcoma virus (KRAS) mutations were detected in 32.3% (10/31), 35.7% (5/14), and 7.1% (2/28) of patients with ICC, ECC, and GBC, respectively. Patients with GBC had a lower incidence of KRAS mutations than those with cholangiocarcinoma (7% vs. 33%, p=0.011). Finally, TP53 mutations were detected in 32.3% (10/31), 71.4% (10/14), and 53.6% (15/28) of patients with ICC, ECC, and GBC, respectively.

DISCUSSION

EUS-TA is a useful diagnostic method for BTC. Since most BTCs are unresectable at diagnosis, tissue samples must be obtained in an alternative manner. Percutaneous liver biopsy is widely used for diagnosis and to obtain samples. However, in this study, only 65% of the samples obtained in this manner were adequate for CGP analysis. However, 86% of the samples obtained using 22-G or 19-G FNB needles were adequate for CGP. EUS-TA enables the collection of samples not only from liver lesions, but also from lymph nodes and gallbladder walls more easily than percutaneous biopsy.

Transpapillary tissue sampling is a good method for diagnosis, but its sensitivity is 48.1%\(^1\) and such samples may involve normal biliary duct epithelium. This may reduce the tumor cellularity of the samples, therefore, transpapillary samples were not used for tissue-based CGP.

Since the genetic analysis of samples obtained using EUS-TA was first reported in 2001,\(^2\) its use has become widespread. The pancreas (65%) and lungs (26%) are the most common sites of primary tumors among patients undergoing EUS-TA.\(^3\) However, very few reports have been published on the genetic analysis of BTC samples obtained using EUS-TA.

The first report of genetic analysis of BTC using specimens obtained through EUS-FNA was published in 2019. Therein, Hirata et al.\(^4\) reported that 95.2% (20/21) of EUS-FNA samples were successfully analyzed using 22-G (n=19) or 25-G needles (n=2) (Expect or Acquire, Boston Scientific). The Iron AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific) was used for genomic analysis.

To the best of our knowledge, ours is the first report on the genetic analysis of EUS-TA samples using genomic panel tests, such as the Foundation One CDx and OncoGuide NCC Oncopanel System, in a clinical setting. In this study, 76.5% (39/51) of the EUS-TA samples and 85.7% (36/42) of those obtained using 22-G or 19-G FNB needles were adequate for CGP analysis. Moreover, samples obtained using 22-G or 19-G FNB yielded a high adequacy rate, similar to that of surgical specimens.

Other primary tumors, including pancreatic cancers, may also be sampled for CGP. Ikeda et al.\(^5\) revealed that 19-G needles (19-G vs. 22-G: 56% vs. 23%, p<0.001) and FNB needles (FNB vs. FNA: 48% vs. 11%, p<0.001) were significantly and positively associated with the adequacy of the OncoGuide NCC Oncopanel System. In their study, the multivariate analysis
revealed that the independent factors associated with adequacy were needle gauge (19-G; odds ratio [OR], 2.53; 95% CI, 1.15–5.57; p=0.021) and needle type (FNB; OR, 3.57; 95% CI, 1.05–12.20; p=0.041).

Takahashi et al. also reported that the amount of tissue obtained by 19-G FNB was approximately three times larger than that obtained by 19-G FNA (median 15.20 mm² vs. 5.44 mm², p=0.010) and that obtained by 22-G FNB (median 15.20 mm² vs. 4.49 mm², p=0.008). Both studies indicated that 19-G and FNB needles were preferred over other needles for patients with pancreatic cancer. Our results were consistent with previous results in that large-gauge and FNB needles had a significant association with adequacy (19-G vs. 22-G; 93% vs. 55%, p=0.0021; and FNB vs. FNA: 84% vs. 33%, p=0.013).

In the present study, IDH1 mutations and FGFR2 fusions were detected in patients with ICC, and ERBB2 amplifications were detected in patients with GBC. According to previous reports, the prevalence of IDH1 mutations and FGFR2 fusions is 13.1% and 9% to 14%, respectively, among patients with ICC, and that of ERBB2 amplifications is 12.8% among patients.
with GBC. These three targetable alterations were the most frequently detected alterations among patients with BTC in the current study. Israel et al. demonstrated that, among patients with ICC, FGFR2 fusions were detected less frequently in liquid biopsies than in tumor tissues.

Berchuck et al. reported on the clinical landscape of cell-free DNA (cfDNA) alterations in patients with advanced BTC. The landscape of cfDNA (n=1671) and tissue (n=349, ACR Project GENIE database of metastatic BTC) differed significantly in terms of the detection of FGFR2 fusions. No significant differences in the frequencies of IDH1 mutations or ERBB2 amplifications were observed between cfDNA and tissue samples in this study. Therefore, we believe that tissue-based CGP is preferable to liquid-based CGP for detecting FGFR2 fusions. Furthermore, pemigatinib has been approved in Japan since 2022, and tissue-based CGP is preferred especially for patients with ICC.

This study had some limitations. First, this was a retrospective, single-center study. Second, there was a risk of selection bias. Third, there might have been some cases in which tissue-based CGP could be performed; however, CGP was not performed because the pathologists judged the samples to be inadequate for analysis. In the future, we need to perform a multicenter study with a large cohort of patients with BTC to investigate the efficacy of tissue-based CGP using samples obtained by EUS-TA and to identify the factors associated with sample adequacy.

In conclusion, EUS-TA is safe for obtaining tissue samples for CGP. Factors significantly positively associated with adequacy were the use of 22-G or 19-G FNB needles, a target size ≥30 mm, the target of primary lesions, and the number of punctures. Patients with BTC frequently exhibit druggable genetic alterations, with FGFR2 fusions detected more frequently than other alterations in tissue samples. We believe that EUS-TA is useful for tissue-based CGP of BTC, particularly in patients with ICC.

Conflicts of Interest
Dr. Mizuno reports grants and fees from Yakult Honsha, Novartis, MSD, Ono Pharmaceutical, ASLAN Pharmaceuticals, Incyte, Seagen, Taiho Pharmaceutical and Dainippon Sumitomo Pharma.; none of the grants are connected with the submitted work. The other authors have no potential conflicts of interest.

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Author Contributions
Conceptualization: TaY, KH; Data curation: TaY; Investigation: TaY; Methodology: KH; Project administration: KH; Resources: TaY, SH, TK, NO, YK, NM, MY, SI, TsY; Supervision: KH; Visualization: TaY; Writing—original draft: TaY; Writing—review & editing: all authors.

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REFERENCES


The role of needle-based confocal laser endomicroscopy in the diagnosis of pancreatic neuroendocrine tumors

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nCLE combined with EUS-FNA can be performed safely and easily for PNETs. Although the diagnostic performance of EUS-FNA for PNETs is high, nCLE may be a diagnostic option in cases of inconclusive EUS-FNA findings.

nCLE FNA nCLE+FNA

Surgery

FNA

EUS
INTRODUCTION

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is the gold standard technique for diagnosing pancreatic neuroendocrine tumors (PNETs); however, some PNETs are difficult to diagnose. Recently, the efficacy of needle-based confocal laser endomicroscopy (nCLE) in diagnosing solid pancreatic masses has been reported. However, the efficacy of nCLE in the diagnosis of PNETs remains unknown and only a small number of cases have been reported. Hence, this study aimed to evaluate the efficacy of nCLE in the diagnosis of PNETs.

Methods: This single-center retrospective study evaluated 30 consecutive patients with suspected PNETs on contrast-enhanced computed tomography, who consented to nCLE combined with EUS-FNA and were diagnosed using EUS-FNA or surgical resection. The diagnostic criteria for PNETs using nCLE were based on the nesting and trabecular and glandular arrangement of tumor cell clusters surrounded by capillary vessels and fibrosis, as reported in previous studies.

Results: The diagnosis using nCLE was classified into three categories: misdiagnosis in three cases (10%), non-diagnostic in six cases (20%), and diagnostic in 21 cases (70%). nCLE was able to diagnose PNET in one of the two cases with inconclusive EUS-FNA.

Conclusions: Although further development of the resolution and optimization of the diagnostic criteria are required, nCLE may constitute a useful diagnostic option in cases of inconclusive EUS-FNA for PNETs.

Keywords: Diagnosis; Endoscopy; Fine-needle aspiration; Neuroendocrine tumor; Pancreas

Background/Aims: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a highly accurate method for diagnosing pancreatic neuroendocrine tumors (PNETs); however, some PNETs are difficult to diagnose. Recently, the efficacy of needle-based confocal laser endomicroscopy (nCLE) in diagnosing solid pancreatic masses has been reported. However, the efficacy of nCLE in the diagnosis of PNETs remains unknown and only a small number of cases have been reported. Hence, this study aimed to evaluate the efficacy of nCLE in the diagnosis of PNETs.

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Results: The diagnosis using nCLE was classified into three categories: misdiagnosis in three cases (10%), non-diagnostic in six cases (20%), and diagnostic in 21 cases (70%). nCLE was able to diagnose PNET in one of the two cases with inconclusive EUS-FNA.

Conclusions: Although further development of the resolution and optimization of the diagnostic criteria are required, nCLE may constitute a useful diagnostic option in cases of inconclusive EUS-FNA for PNETs.

Keywords: Diagnosis; Endoscopy; Fine-needle aspiration; Neuroendocrine tumor; Pancreas

nCLE combined with EUS-FNA procedure

In all patients, nCLE combined with EUS-FNA was performed...
under conscious sedation using 5 to 10 mg of intravenous midazolam (Astellas) and 35 mg of intravenous pethidine hydrochloride (Mitsubishi Tanabe Pharma.). EUS was performed using a Prosound SSD α-10 (Hitachi Ltd.), EU-ME2 (Olympus Corporation), SU-1 (Fujifilm Corporation), or ARIETTA850 (Hitachi Ltd.) ultrasound systems with either a GF-UCT260 curved linear echoendoscope (Olympus Corporation) or EG-580UT curved linear echoendoscope (Fujifilm Corporation).

Initially, the AQ-Flex 19 probe (Cellvizio; Mauna Kea Technologies) was preloaded into a 19-gauge EUS needle (Expect Slimline; Boston Scientific Corporation). The pancreatic tumor was punctured, and the nCLE probe was locked 2 mm above the tip. Sodium fluorescein was injected immediately after the target was punctured. The nCLE provided real-time images. The acquisition time was usually limited to 10 minutes. The needle position was changed using the fanning technique as appropriate to obtain specific images.

After the nCLE examination, EUS-FNA was performed using the slow-pull method. EUS-FNA was performed using 22- or 25-gauge needles (EZ shot 3 plus; Olympus Corporation or Acquire; Boston Scientific) as needed.

Definitions
The primary endpoint of this study was the accuracy of nCLE for PNET diagnosis. The diagnosis of PNETs was based on a larger series of nCLE in solid pancreatic masses that were presented at the United European Gastroenterology Week meeting in 2014. The typical findings of PNETs are nesting, trabecular, and glandular arrangements of tumor cell clusters surrounded by capillary vessels and fibrosis. These findings were consistent with the histological structure (Fig. 1). The secondary endpoints were adverse events and factors affecting nCLE accuracy. Adverse events that were possibly related to the procedure and that occurred after the procedure were described in accordance with the American Society for Gastrointestinal Endoscopy lexicon. The maximal section of the resected specimens was used to evaluate the degree of stromal fibrosis. 'Rich fibrosis' was noted when stromal fibrosis occupied >30% of the total tumor area.

Continuous variables were analyzed using the Mann-Whitney U-test. Categorical variables were analyzed using Fisher exact test. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Ethical statements
This study was approved by the institutional review board of our institution (approval no. 2022-0-207). Each patient provided informed consent to undergo EUS-FNA and nCLE.

RESULTS
The study included 15 males (50.0%) and 15 females (50.0%). The patients’ ages ranged from 38 to 76 years (median, 60 years). Pancreatic tumors were located in the body (n=13, 43.3%), head (n=9, 30.0%), or tail (n=8, 26.7%) of the organ. Median tumor size was 10.0 mm (range, 5.3–60.0 mm). Seven lesions (23.3%) contained cystic components. The final diagnosis was achieved using surgical resection or EUS-FNA in 19 (63.3%) and 11 (36.7%) cases, respectively. Regarding grading, 27 PNETs were classified as G1 or G2 in 25 (83.3%) and 2 (6.7%) cases, respectively. The remaining three cases were diagnosed using EUS-FNA, but the grading was unclassified (Table 1).

![Fig. 1](image-url) Typical needle-based confocal laser endomicroscopy images of pancreatic neuroendocrine tumors (PNETs). (A) Typical findings of PNETs. (B) Nesting, trabecular, and glandular arrangements of tumor cell clusters. (C) Surrounding capillary vessels and fibrosis. (D) These findings are consistent with the histological structure (hematoxylin and eosin staining, ×400).
The needles used for EUS-FNA were FNA needles in 10 patients (33.3%) and FNB needles in 20 patients (66.7%). The median number of punctures was 2 (range, 1–5). The mean acquisition time for nCLE was 269 seconds (range, 90–640 seconds). The accuracies of EUS-FNA were 90.0% with the FNA needle and 95.0% with the FNB needle. The accuracy of nCLE was 70.0%, which was significantly lower than that of EUS-FNA alone. However, in one of the two cases with inconclusive EUS-FNA results, the nCLE was able to diagnose PNET. The accuracy of nCLE combined with EUS-FNA was 96.7%. No adverse events were observed. Fluorescein was well tolerated by all patients (Table 2).

Among the 30 cases, nCLE results were classified as a misdiagnosis, non-diagnostic, and diagnostic in 3 (10%), 6 (20%), and 21 cases (70%), respectively. Among the patients, there was a 50-year-old male with an 8-mm pancreatic body lesion that was inconclusive on EUS-FNA (Fig. 2). The two misdiagnosed cases were diagnosed as SCNs due to superficial vascular network-like findings observed on nCLE or a small number of cells in the vascular bundle. In the six non-diagnostic cases, there were findings indicating PNETs and other pancreatic tumors on nCLE; only isolated small dark cells or fine white fibrous bands were observed (Fig. 3). In four misdiagnosed and non-diagnostic cases, surgical resection was performed (Table 3), and the tumors in all cases had rich stromal fibrosis in the surgical specimens. For example, Case 1 from Table 3 is presented in Figure 4. Univariate analyses were conducted to identify the factors affecting the accuracy of nCLE. MRI-T2-weighted imaging (MRI-T2 WI) findings constituted a significant clinical factor affecting the accuracy of nCLE. Tumor location, tumor size, presence of cystic components, and CE-EUS findings were not found to be significant clinical factors (Table 4). Grading was a significant pathological factor affecting the accuracy of nCLE. The presence of a clear border, intraductal pancreatic extension, cystic components, and the degree of stromal fibrosis were not found to be significant pathological factors (Table 5).

**DISCUSSION**

This retrospective study investigated the diagnostic performance and safety of EUS-guided nCLE for PNET. To our knowledge, this is the first report to evaluate the diagnostic yield of nCLE for PNETs in a relatively large sample of patients.

Regarding the safety of nCLE combined with EUS-FNA, because nCLE is performed using FNA needles, no problems beyond the known adverse events related to EUS-FNA should be expected. Additionally, adverse events associated with the intravenous administration of fluorescein are considered mild and transient. No adverse events were found in this study, similar to previous studies on nCLE for solid pancreatic masses. Although nCLE requires exclusive equipment and is costly, it can be performed easily and safely in combination with EUS-FNA.
Fig. 2. A case of inconclusive endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). (A, B) The lesion is detected in the pancreatic body using enhanced computed tomography and EUS. (C) The needle-based confocal laser endomicroscopy image shows typical findings of pancreatic neuroendocrine tumor (PNET). (D) EUS-FNA shows no tumor cells in the cell block (×100). (E) Histopathological view of the surgical specimen (hematoxylin and eosin staining, ×20). (F) The pathological diagnosis is PNET, G1. F-1: hematoxylin and eosin staining, ×100; F-2: synaptophysin is positive, ×100; F-3: chromogranin A is positive, ×100; F-4; Ki-index is <1%, ×100.

Fig. 3. Needle-based confocal laser endomicroscopy images of misdiagnosed and non-diagnostic cases. (A) Superficial vascular network. (B) Small cells with vascular bundles. (C) Small dark cells that are isolated. (D) Fine white fibrous bands.

In this study, the accuracy of nCLE for the diagnosis of PNETs was 70.0%, which was not satisfactory. Typical PNETs are detected as hypervascular tumors on contrast-enhanced CT. Hence, differentiating them from SCNs and SPNs is of crucial importance. Typical findings of SCNs and SPNs are superficial vascular networks and small cells with white stromal bands, respectively. In the two misdiagnosed cases of SCNs, the hypervascular areas were identified as superficial vascular networks. In one misdiagnosed SPN case, areas of rich stromal fibrosis and a few tumor cells were identified as small cells with white stromal bands. It is critical to consider that even in PNETs, nCLE images characteristic of SPNs and SCNs may be observed. In surgical cases among the misdiagnosed and non-diagnostic cases, the characteristic arrangement of
Table 3. Detailed characteristics of misdiagnosed and non-diagnostic cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Location</th>
<th>Size (mm)</th>
<th>Cystic component</th>
<th>nCLE diagnosis</th>
<th>Final diagnosis achieved</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>59</td>
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<td>Tail</td>
<td>8.5</td>
<td>−</td>
<td>No typical finding</td>
<td>Surgical resection</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>Female</td>
<td>Body</td>
<td>10.2</td>
<td>−</td>
<td>SCN</td>
<td>EUS-FNA</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>Male</td>
<td>Head</td>
<td>56.7</td>
<td>−</td>
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<td>Surgical resection</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
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<td>Head</td>
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<td>−</td>
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<td>EUS-FNA</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>Female</td>
<td>Body</td>
<td>6.4</td>
<td>−</td>
<td>No typical finding</td>
<td>Surgical resection</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Female</td>
<td>Tail</td>
<td>40.1</td>
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<td>SPN</td>
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<tr>
<td>7</td>
<td>76</td>
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<td>+</td>
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<tr>
<td>8</td>
<td>42</td>
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<td>EUS-FNA</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
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<td>Body</td>
<td>8.3</td>
<td>−</td>
<td>No typical finding</td>
<td>EUS-FNA</td>
</tr>
</tbody>
</table>

nCLE, needle-based confocal laser endomicroscopy; SCN, serous cystic neoplasm; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; SPN, solid pseudopapillary neoplasm; −, absence of cystic components.

tumor cells was only observed in small areas due to the presence of rich stromal fibrosis, and nCLE was unable to detect the findings. The diagnosis of PNET by EUS-FNA is based on the presence of small round cells on hematoxylin and eosin staining in combination with immunohistochemistry showing the expression of chromogranin A and synaptophysin. Therefore, even cases with rich stromal fibrosis can be diagnosed if the tumor cells are collected. Conversely, nCLE cannot be diagnosed unless characteristic arrangements of tumor cell clusters are observed. In this study, to evaluate the association between the diagnostic performance of nCLE and stromal fibrosis, we examined the degree of stromal fibrosis in surgical specimens as a pathological factor and the findings of MRI-T2 WI as a clinical factor. We considered the findings of MRI-T2 WI as a clinical factor because it has been reported that most PNETs are hyperintense on MRI-T2 WI, but PNETs with rich stromal fibrosis appear isointense or hypointense.11,21 The present results suggest that the findings of MRI-T2 WI were a significant clinical factor affecting the accuracy of nCLE, and the accuracy of nCLE in cases with isointense or hypointense findings was lower than that in cases with hyperintense findings. The degree of stromal fibrosis was not a significant pathological factor affecting the accuracy of nCLE. However, the accuracy of nCLE in cases with poor stromal fibrosis was 100%, whereas the accuracy of nCLE in cases with rich stromal fibrosis was 63.6%, which may not have been a significant factor owing to the small number of cases. Hijioka et al. reported that tumors with rich stromal fibrosis have a lower diagnostic yield on EUS-FNA than tumors with minimal fibrosis,11 which may be more pronounced in nCLE. How can the diagnostic performance of nCLE be improved in such cases? The fanning technique is useful for obtaining diagnostic findings from nCLE. However, the fanning technique is difficult to apply for small lesions.

In contrast, when the tumor is too small to allow for inadequate sampling by EUS-FNA, nCLE is useful because tissue sampling is not required. Such a case was presented in this study. Furthermore, cystic PNETs are considered good candidates for nCLE for the same reason. Although there were no...
yses of factors affecting the accuracy of nCLE, the location of the tumor, size of the tumor, and presence of cystic components were not found to be significant factors that may enable the diagnosis of pancreatic lesions without tissue sampling. Grading was a significant independent factor affecting the accuracy of nCLE; however, there were only two G2 cases, and these two cases were characterized by rich stromal fibrosis. It is possible that nCLE could overcome the limitations of EUS-FNA. However, further studies with larger numbers of cases are required to confirm this hypothesis.

Currently, probe-based confocal laser endomicroscopy (pCLE) is widely used in the gastrointestinal tract, and its efficacy has been reported in several studies.\(^{25-30}\) In contrast, the diagnostic performance of nCLE for pancreatic cystic lesions and solid pancreatic masses has not yet reached the level of pCLE. nCLE has a smaller outer diameter and lower resolution than pCLE because it is performed through the FNA needle. In addition, nCLE is susceptible to respiratory variability and intratumor heterogeneity of tumor cells. Each of these issues can be addressed to some extent by abdominal compression and changes in the puncture line; however, there are some limitations to this approach. Further developments in the resolution and optimization of diagnostic criteria are warranted to improve the diagnostic performance of combined nCLE.

The limitations of this study include its retrospective design and the fact that it was performed at a single center with a small number of patients. Another limitation is that the final diagnosis was achieved not only by surgical resection but also by EUS-FNA. In addition, nCLE is susceptible to respiratory variability and intratumor heterogeneity of tumor cells. Each of these issues can be addressed to some extent by abdominal compression and changes in the puncture line; however, there are some limitations to this approach. Further developments in the resolution and optimization of diagnostic criteria are warranted to improve the diagnostic performance of combined nCLE.

The limitations of this study include its retrospective design and the fact that it was performed at a single center with a small number of patients. Another limitation is that the final diagnosis was achieved not only by surgical resection but also by EUS-FNA. In addition, because all the cases were PNETs, the specificity and positive/negative predictive values could not be evaluated. In fact, there were cases with typical findings of PNETs on nCLE that could not be diagnosed or were diagnosed as another tumor by EUS-FNA and were followed up without surgical resection. If such cases were diagnosed as PNETs by surgical resection, the diagnostic yield of nCLE would have a different outcome.

In conclusion, nCLE combined with EUS-FNA can be performed safely and easily for PNETs. Although the diagnostic performance of EUS-FNA for PNETs is high, nCLE may be a diagnostic option in cases of inconclusive EUS-FNA findings.

### Conflicts of Interest

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Polyposis of gastrointestinal tract after COVID-19 mRNA vaccination: a report of two cases

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Cronkhite-Canada syndrome is a rare gastrointestinal polyposis syndrome with distinctive clinical features and endoscopic findings. Diagnosis can be challenging without suspicion, and the disease carries high mortality due to complications such as infection, gastrointestinal bleeding, and malignancies. This paper presents two cases of Cronkhite-Canada syndrome occurring after coronavirus disease 2019 (COVID-19) mRNA vaccination. Both cases exhibited typical clinical findings, including hypogeusia, onychodystrophy, alopecia, and weight loss. Typical polyposis in the gastrointestinal tract was confirmed through endoscopies. As symptomatic treatment did not improve the symptoms, corticosteroids were administered, and symptoms and laboratory test results improved immediately. The patients improved upon corticosteroids tapering. These cases illustrate typical presentations of Cronkhite-Canada syndrome and the course of the disease following corticosteroid treatment. Additionally, they suggest the possibility that Cronkhite-Canada syndrome may be triggered by COVID-19 mRNA vaccination.

Keywords: Adverse drug event; COVID-19; Intestinal polyposis; Vaccines

INTRODUCTION

Cronkhite-Canada syndrome is a rare gastrointestinal polyposis syndrome with distinctive clinical features and endoscopic findings. Diagnosis can be challenging without suspicion, and the disease carries high mortality due to complications such as infection, gastrointestinal bleeding, and malignancies.

We report two cases of Cronkhite-Canada syndrome that occurred after coronavirus disease 2019 (COVID-19) mRNA vaccination, providing detailed endoscopic images. The institutional review board’s approval was waived by our hospital’s ethics committee. The study was performed according to the principles of the Declaration of Helsinki, and we obtained the patients’ written consent for this study.

CASE REPORTS

Case 1

A 61-year-old woman presented with chronic watery diarrhea lasting 2 months. Diarrhea occurred 5 to 10 times a day and often contained blood and pus. Periumbilical pain, hypogeusia, anorexia, nausea, dyspepsia, and weight loss accompanied. The symptoms began 3 days after COVID-19 mRNA booster vaccination (Moderna). She had no underlying disease and denied intake of supplements or herbal medications.

Physical examination revealed a dehydrated tongue, diffuse abdominal tenderness without peritoneal irritation, alopecia, and onychodystrophy (Fig. 1). Blood tests were unremarkable, except for hypoalbuminemia and hypokalemia. Computed tomography revealed diffuse wall thickening of the stomach and colon without enlarged lymph nodes. The esophagogastroduo-
denoscopy and ileocolonoscopy revealed numerous erythematosous polyps in the stomach (Fig. 2A) and colon (Fig. 2B) and atrophied villi in the duodenum (Fig. 2C) and terminal ileum (Fig. 2D). Histology reports of polyps revealed chronic active inflammation with glandular distension, interstitial edema, and a crypt abscess. *Helicobacter pylori* and cytomegalovirus were negative.

She was diagnosed with Cronkhite-Canada syndrome. As the symptoms did not improve with 10 days of symptomatic treatments, including intravenous nutrition, hydration, and anti-diarrheal medication, a corticosteroid was administered (prednisolone, 30 mg/day), and the symptoms improved in a few days. The corticosteroids were tapered over 8 weeks.

Alopecia and onychodystrophy improved. Diarrhea improved and worsened repeatedly, but overall, it improved, and the lost weight was regained. Six months later, she presented no symptoms, and most of the polyps in the stomach and colon disappeared on the follow-up esophagogastroduodenoscopy (Fig. 3A) and ileocolonoscopy (Fig. 3B).

**Case 2**

A 63-year-old woman presented with chronic watery diarrhea lasting 1 month. Diarrhea occurred more than five times a day and often contained blood and pus. Periumbilical pain, hypoesthesia, anorexia, nausea, dyspepsia, and weight loss accompanied. The symptoms began 2 months after COVID-19 mRNA booster vaccination (Pfizer). She had no underlying disease and denied taking supplements or herbal medications.

Physical examination revealed a dehydrated tongue, diffuse abdominal tenderness without peritoneal irritation, alopecia, and onychodystrophy (Fig. 4). Blood tests were unremarkable, except for hypoalbuminemia and hypokalemia. Computed tomography displayed diffuse wall thickening of the stomach and colon without enlarged lymph nodes. The esophagogastrroduodenoscopy and ileocolonoscopy revealed numerous erythematous polyps in the stomach (Fig. 5A) and colon (Fig. 5B), atrophied villi in the duodenum (Fig. 5C), and edematous
villi in the terminal ileum (Fig. 5D). Histology reports of polyps revealed chronic active inflammation with glandular distension and a crypt abscess. *H. pylori* and cytomegalovirus were negative.

She was diagnosed with Cronkhite-Canada syndrome. As the symptoms did not improve after two weeks of symptomatic treatments, including intravenous nutrition, hydration, and anti-diarrheal medication, a corticosteroid was administered (prednisolone, 30 mg/day) and the symptoms immediately improved. The corticosteroid was tapered over 8 weeks without recurrence of symptoms, and the lost weight was regained. However, a follow-up endoscopy was not performed as she did not return to our hospital.

**DISCUSSION**

Cronkhite-Canada syndrome is a rare disease with hundreds of cases reported worldwide. The disease is characterized by hamartomatous polyposis of the gastrointestinal tract, except for the esophagus. The condition typically presents with chronic diarrhea accompanied by hypoguesia, onychodystrophy, alopecia, abdominal discomfort, xerostomia, skin hyperpigmentation, and weight loss. While the etiology is unknown, autoimmune reactions are suggested to contribute to the disease’s pathogenesis. Stress, *H. pylori* infection, and allergic reactions to Chinese alternative medications were reported as possible triggers.

There is no standard treatment for the disease. However, corticosteroids, infliximab, azathioprine, and 5-aminosalicylate have been reported to have a positive effect in severe cases. Gastrointestinal bleeding, malnutrition, and infection are major causes of death, and the patients are at substantial risk for gastrointestinal malignancies. This paper presents two cases of Cronkhite-Canada syndrome occurring after COVID-19 mRNA vaccination. In both cases, typical clinical findings, such as hypoguesia, onychodystrophy, alopecia, and weight loss were observed. In addition, typical polyposis in the gastrointestinal tract was confirmed through endoscopies. Symptomatic treatments did not improve the symptoms, prompting the administration of corticosteroids, resulting in immediate improvement of symptoms and laboratory test results. The patients improved upon corticosteroids tapering and have not present recurrence of symptoms to date.

There is no established consensus on the pathogenesis of Cronkhite-Canada syndrome. However, immune dysregulation has been implicated because the disease is commonly accompanied by conditions such as hypothyroidism and systemic lupus erythematosus and serology commonly reveals antinuclear antibody positivity. Furthermore, case reports suggest the potential association of the disease with IgG4-related disease, due to the favorable response to corticosteroid therapy.

![Fig. 4. Onychodystrophy of the Case 2 patient's fingernails.](image1)

![Fig. 5. Endoscopic findings of the Case 2 patient's gastrointestinal tract. (A) Numerous erythematous polyps in the stomach. (B) Numerous erythematous polyps in the colon. (C) Atrophied villi in the duodenum. (D) Dilated villi in the terminal ileum.](image2)
Even though the exact pathological mechanism remains unknown, previous studies suggest that COVID-19 infection could trigger autoimmunity by inducing rapid autoinflammatory dysregulation in genetic predisposed individuals. A retrospective study from China reported a 20-50% prevalence of autoantibodies in patients with COVID-19 infection. The cross-reaction between SARS-CoV-2 proteins and antigens in the human cardiovascular, gastrointestinal, and nervous systems has been suggested as a mechanism by which various autoimmune diseases occur in patients infected with COVID-19. There has been a case report of a 40-year-old female diagnosed with Cronkhite-Canada syndrome accompanied by Entamoeba histolytica and COVID-19 infection in Nepal. She reported diffuse abdominal pain, hematochezia, diarrhea, nausea, weight loss, alopecia, onychodystrophy, and hyperpigmentation of the skin, which improved drastically after 4 weeks of corticosteroid therapy. Although the exact mechanism of post-infection Cronkhite-Canada syndrome development is under scrutiny, there have been reports of cases accompanied with infectious diseases that improved with antibiotic treatment. Therefore, the report suggests Cronkhite-Canada syndrome should be suspected in patients with infectious disease if typical symptoms of Cronkhite-Canada syndrome are present.

Whether the association between the COVID-19 mRNA vaccine and autoimmune diseases is coincidental or causal remains to be elucidated. Increased risk of Guillain-Barre syndrome with swine influenza vaccination, and that of idiopathic thrombocytopenia with the measles-mumps-rubella vaccination was confirmed by several studies. Case reports on new-onset autoimmune diseases, such as immune thromboctopenic purpura, systemic lupus erythematosus, autoimmune liver diseases, and Guillain-Barre syndrome have also increased after COVID-19 mRNA vaccination. A 65-year-old male case of Cronkhite-Canada syndrome after COVID-19 mRNA booster vaccination (Pfizer) was reported in Japan. Alopecia, onychodystrophy, and hypoguesia started 4 weeks after the vaccination. As the result of reverse transcription polymerase chain reaction for COVID-19 was negative, the patient was initially diagnosed with a COVID-19 vaccination-related condition, as the symptoms commonly appeared in patients with COVID-19 infection. Eventually, Cronkhite-Canada syndrome was diagnosed as polyposis, which was observed at colonoscopy, and the symptoms improved after corticosteroid treatment. While symptoms of adverse effects of COVID-19 vaccination are similar to those of Cronkhite-Canada syndrome, the report suggested that if symptoms such as alopecia, hypoguesia, or weight loss occur after COVID-19 vaccination, the possibility of Cronkhite-Canada syndrome should be suspected. In our cases report, there is a difference in the timing of symptom onset after COVID-19 mRNA booster vaccination. It is difficult to confirm the exact onset in each patient because the possibility that the disease continued in the subclinical period and worsened after booster vaccination cannot be ruled out.

We report two typical cases of Cronkhite-Canada syndrome and the course of the disease following corticosteroid treatment. Although the casual association between Cronkhite-Canada syndrome and COVID-19 infection or vaccination remains unclear, the cases suggest the possibility that Cronkhite-Canada syndrome may be triggered by COVID-19 mRNA vaccination in genetically susceptible individuals. Therefore, Cronkhite-Canada syndrome must be differentiated in such patients with typical symptoms, considering the excellent response to corticosteroid treatment and the poor prognosis of the disease.

Conflicts of Interest
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REFERENCES


A 65-year-old female visited the emergency room due to sudden hematemesis and hematochezia. One year earlier, the patient underwent endovascular implantation of an aorto-bi-iliac bifurcation stent graft for a fusiform infrarenal aortic aneurysm that extended to the left common iliac artery. At the time of presentation, her blood pressure and heart rate were 70/40 mmHg and 105 beats/min, respectively. Laboratory findings showed a white blood cell count of 13,000/μL, hemoglobin level of 8.0 g/dL, and platelet count of 405,000/μL. Emergent endoscopy identified a foreign material (an aortic stent graft) with vascular pulsation in the third part of the duodenum (Fig. 1). Abdominal computed tomography revealed increased fat stranding around the aorta, which is indicative of inflammation, and a loss of the fat plane between the duodenum and aorta (Fig. 2). Therefore, the cause of bleeding was diagnosed as an aortoduodenal fistula caused by the previously placed aortic stent graft. The patient underwent primary closure of the duodenal perforation and omental wrapping and was discharged without any complications. However, the patient passed away 31 months later due to recurrence of the aortoduodenal fistula.

Aortoenteric fistula can occur secondary to aortic reconstruction procedures and can develop anywhere in the gastrointestinal tract adjacent to the aorta; however, it is most frequently observed in the third part of the duodenum, which is anchored in the retroperitoneal space and positioned directly anterior to the aorta. The location of the duodenum in close proximity to the aorta makes it susceptible to fistula formation due to the constant transmission of pulsatile forces from the aorta. Therefore, aortoduodenal fistula should be considered a potential cause of hematemesis or hematochezia in patients with a history of aortic stent graft.
Conflicts of Interest
Gwang Ha Kim is currently serving as a deputy editor for Clinical Endoscopy; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. Seunghyun Hong has no potential conflicts of interest.

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Fig. 2. Abdominal computed tomography reveals increased fat stranding around the aorta, which is indicative of inflammation, and a loss of the fat plane between the duodenum and aorta (arrows). (A) Pre-enhanced phase. (B) Arterial phase.

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REFERENCES
Effective hemostasis under gel immersion endoscopy using inflated balloons on the tip of double balloon endoscope for active bleeding in the small intestine

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Securing an endoscopic visual field when identifying the source of gastrointestinal bleeding is difficult because the injected water easily mixes with blood and residue. Performing endoscopic procedures is challenging when the luminal contents are displaced by gas insufflation, which leads to significant discomfort. Gel immersion endoscopy (GIE) using an electrolyte-free gel (VISCOCLEAR; Otsuka Pharmaceutical Factory) has been reported to be useful for securing the visual field during endoscopy for gastrointestinal bleeding.1,2 Particularly in the case of the small intestine, which is frequently filled with blood, GIE is effective for narrow lumens. This gel can easily replace the blood. Insufflation of the endoscope balloon avoids backflow of the gel, enabling it to push away blood and hold the intestinal wall, allowing the endoscope to stay at the targeted position. We also used a BioShield irrigator (US Endoscopy), which allowed additional injection of the gel with a therapeutic device through the accessory channel. In addition, the use of a transparent cap makes it easier to concentrate the gel in front of the endoscope (Fig. 1). Herein, we report the successful treatment of a hemangioma with active bleeding in the small intestine under GIE using inflated balloons on the tip of a double balloon endoscope (DBE).

A 15-year-old boy had been suffering from melena for a month. Esophagogastroduodenoscopy and colonoscopy failed to reveal any signs of active bleeding. Capsule endoscopy was performed to check for small intestinal lesions and detected bloody intestinal fluid in the jejunum, followed by DBE, which revealed a large amount of fresh blood in the jejunum (Fig. 2). The cause of gastrointestinal bleeding was undetectable because...
the injected water was mixed with blood and the endoscope did not remain at the targeted position. However, by applying GIE using inflated balloons on the tip of the DBE, the visual field was secured, and the bleeding source was detected (Fig. 3, Supplementary Video 1). We immediately injected a hypertonic saline-epinephrine solution at the point of bleeding. Moderately active bleeding allowed us to secure the visual field. We were able to identify the lesion suspicious for a hemangioma as the source of bleeding, which was further performed with complete hemostasis using endoclips (SureClip; Microtech) (Fig. 4). In this case, approximately 80 mL of gel was used. The patient was discharged without complications, and has not suffered from recurrence.

In conclusion, GIE using inflated balloons on the tip of DBE is useful for precise treatment of active gastrointestinal bleeding, for it could facilitate endoscopic maneuvers and allow clear endoscopic view.
Supplementary Material


Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.146.

Conflicts of Interest
The authors have no potential conflicts of interest.

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Author Contributions
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Use of an endoscopic powered debridement device for treatment of post-surgical fatty pancreatic necrosis

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Acute pancreatitis can progress to necrosis of the pancreatic tissue and/or peripancreatic tissue which will require intervention if the necrosis becomes infected. Alternatively, a feared adverse event of performing a distal pancreatectomy is the development of a pancreatic leak, which can lead to pancreatic fluid collections. While traditional management entailed utilization of percutaneous drains or re-operation, endoscopic transmural drainage offers another treatment option for these collections.

We describe a case of utilizing endoscopic powered debridement devices to treat a large post-operative collection with primarily fatty contents. Consent was obtained from the patient for submission of this case report.

A 71-year-old man with a history of pancreatic neuroendocrine tumor status post distal pancreatectomy developed a large walled-off pancreatic necrosis (WOPN) collection. He initially underwent dual-modality drainage via endoscopic ultrasound-guided cystogastrostomy with a lumen-apposing metal stent (LAMS) and percutaneous drain placement. Due to the increasing size of the collection, we performed direct endoscopic necrosectomy (DEN).

The entrance through the LAMS revealed a large cavity filled with fatty necrotic tissue and copious amounts of oil droplets (Fig. 1, Supplementary Video 1). Necrosectomy using a snare proved unsuccessful as the snare could not grasp sufficiently large pieces. A 3.2-mm powered debridement device (EndoRobot; Interscope Inc.) was then used to perform necrosectomy (Fig. 2), which was partially successful in clearing the cavity. In the subsequent procedure, a 6.0-mm debridement device (Fig. 3) was utilized (Supplementary Video 1), which led to the significant removal of large amounts of necrotic tissue from the cavity. Using a percutaneous drain as a guide, the necrosectomy was successful in clearing the cavity down the left paracolic gutter and into the pelvis. At the conclusion of the procedure, a percutaneous drain was placed to continue drainage of the cavity.

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small amount of necrotic tissue and a large amount of pink viable tissue were observed within the cavity (Fig. 1D).

DEN has emerged as a standard treatment for WOPN that does not respond to drainage alone. Technical challenges in DEN include the lack of effective tools for removing or grasping necrotic tissue. The powered debridement device acts as a morcellator, simultaneously cutting and suctioning necrotic debris. Preliminary studies examining the 3.2-mm catheter have demonstrated its safety and efficacy, suggesting that its use may result in fewer procedures than conventional treatment. In an international, multicenter prospective study involving 30 patients with symptomatic WOPN with at least 30% necrosis, DEN with this device led to successful clearance of all necrotic contents in 97% of the participants. Half of the patients had complete clearance within one session with 73% having complete clearance within two sessions. Importantly, this study found no device-related adverse events, although the primary concern with using this device was bleeding, given the possibility of damaging a vessel hidden within the necrotic debris.

Furthermore, larger studies are needed to determine the optimal indications for the use of this debridement device, highlighting the utility of using 3.2- and 6.0-mm catheters to perform DEN in fatty pancreatic necrosis refractory to conventional techniques. We postulate that the lipolytic activity of the ongoing pancreatic leak likely leads to high amounts of fatty necrosis, providing an ideal scenario for the use of a morcellating system.

Supplementary Material

Supplementary Video 1. Direct endoscopy necrosectomy utilizing a powered debridement device (https://doi.org/10.5946/ce.2023.120.v1).

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2023.120.

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A rare colonoscopic finding in a renal transplant recipient

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Quiz

A 50-year-old male visited for colonoscopy screening without any specific symptoms. He received an allogeneic renal transplanta-

tion 20 years prior and had no associated complications. He had undergone colonoscopy three years previously, and there were no abnormal findings. Physical examination revealed no remarkable findings. Blood test results were within normal ranges. Colonoscopy revealed multiple whitish, flat, or slightly elevated mucosal lesions measuring 10 to 20 mm in diameter in the ascending colon. The pit pattern of these lesions was not compatible with that of typical adenomas, and forceps biopsies were preformed at each portion (Fig. 1). Histological findings and immunostaining results for CD68 (PG-M1) are shown in Figure 2. What is the most likely diagnosis?

Fig. 1. Colonoscopy with the use of (A, B) white light and (C, D) narrow-band imaging reveals multiple whitish flat or slightly elevated mucosal lesions measured 10 to 20 mm in diameter at the ascending colon.

Fig. 2. Histopathologic findings. (A) The lesions consist predominantly of histiocytes with eosinophilic granular cytoplasm (von Hansemann cells) (arrows) (hematoxylin and eosin stain, ×200). (B) The lesions are positive for CD68 (PG-M1, ×400).

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The patient was diagnosed with asymptomatic colon malakoplakia, and third-generation cephalosporins were prescribed for 30 days. Colonoscopy performed after six months showed complete resolution of all lesions (Fig. 3).

Malakoplakia is a rare chronic granulomatous disease of uncertain etiology that shows a high incidence in immunocompromised patients with human immunodeficiency virus infection, malignancy, and post-organ transplantation status. Although commonly seen in the urinary tract, it is also reported in other sites, including the gastrointestinal tract, pancreas, liver, lymph nodes, skin, and respiratory tract. Malakoplakia is associated with dysfunctional bacterial clearance by neutrophils and macrophages, and is thus closely related to immunodeficiency. The most commonly reported microorganisms in patients with malakoplakia are *Escherichia coli*, *Proteus*, *Mycobacterium tuberculosis*, and *Staphylococcus aureus*. Clinical manifestations are very diverse and not specific for this disease. Endoscopic findings could be categorized as three different patterns: (1) isolated sessile/polypoid masses in the rectosigmoid colon, (2) diffuse serpiginous lesions or ulcers of the colon, (3) mass occurring in association with cancer of the colon. Diagnosis can be made by histology with the presence of the large granular, eosinophilic histocytes (von Hansemann cells), and more specifically by the laminated, basophilic, targetoid inclusions (Michaelis-Gutmann bodies), which are stained with periodic acid-Schiff, Von Kossa, and Prussian blue. Immunohistochemically, the cells are positive for CD68, CD163 and alpha-chymotrypsin, confirming their histiocytic nature. Medical treatment strategies are based on antibiotics to eradicate microorganisms and cholinergic agonists to enhance macrophage function. Rifampicin and ciprofloxacin have been used for their ability to enter the macrophage. Although their efficacy remains controversial, long-term treatments are recommended.

Physicians should consider malakoplakia when diverse and atypical mucosal lesions are detected on colonoscopy, particularly in immunocompromised patients.

**Conflicts of Interest**

Ji Young Chang is currently serving as a KSGE Publication Committee member in *Clinical Endoscopy*; however, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. Soo Jung Park has no potential conflicts of interest.

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Conceptualization: SJP; Writing–original draft: JYC; Writing–review & editing: all authors.

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Summary of Prescribing information

【Product name in Korea】Promac tablet
【Active ingredient and its content】Polaprezinc (in house) 75mg/tab.
【Indication and usage】1. Gastric ulcer 2. For improvement of gastric mucosal lesion (erosion, bleeding, erythema, edema) induced by acute gastritis and exacerbation of chronic gastritis
【Dosage and administration】The recommended dose for adults is polaprezinc 75mg (1 tab.) twice daily after breakfast and before bedtime
※ Please refer to the package insert for further details. For the latest information, refer to 'Ministry of Food and Drug Safety. (http://drug.mfds.go.kr/)'


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성상
백색~회백색의 분말을 충진한 상부황색, 하부담황색의 캅슐제

효능·효과
1. 활동성 위·십이지장 궤양 치료 및 십이지장 궤양 재발방지 2. 내시경상으로 진단된 미란성 및 궤양성 식도염, 위식도 역류질환(GERD)에 기인한 가슴쓰림(heartburn) 증상의 치료 3. 다음 질환의 위점막병변(미란, 출혈, 발적, 부종)의 개선: 급성위염, 만성위염의 급성 악화기

용법·용량
1. 활동성 위·십이지장 궤양 치료: 성인은 니타지틴으로서 1회 300mg을 1일 1회 취침시에 투여하거나, 1회 150mg을 1일 2회 아침, 저녁으로 경구 투여 한다. 대부분 4주 이내에 치유되지만 필요한 경우 8주까지 투여한다. 활동성 위궤양의 경우 악성여부를 반드시 치료전에 확인해야 한다. 2. 십이지장 궤양 재발방지: 성인은 십이지장 궤양 치유 후 1회 150mg을 1일 1회 취침시에 경구투여한다. 치료는 1년까지 계속될 수 있으며, 그 이상의 장기투여에 대한 결과는 알려져 있지 않다. 3. 위식도역류질환: 성인은 1회 150mg을 1일 2회 아침, 저녁 경구투여한다. 4. 위점막병변 개선: 성인은 1회 150mg을 1일 2회 아침, 저녁으로 경구투여한다. 5. 중증 신장기능 부전 환자를 위한 투여량 조정(제품설명서 참고)

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