

# World Journal of *Gastrointestinal Endoscopy*

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## Endoscopy during COVID-19 pandemic: An overview of infection control measures and practical application

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### Abstract

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in coronavirus disease 2019 (COVID-19) which has affected more than 4.5 million people in 213 countries, and has been declared a pandemic by World Health Organization on March 11, 2020. The transmission of SARS-CoV-2 has been reported to occur primarily through direct contact or droplets. There have also been reports that SARS-CoV-2 can be detected in biopsy and stool specimens, and it has been postulated that there is potential for fecal-oral transmission as well. Gastrointestinal symptoms have been reported in 17.6% of COVID-19 patients and transmission can potentially occur through gastrointestinal secretions in this group of patients. Furthermore, transmission can also occur in asymptomatic carriers or patients with viral shedding during the incubation period. Endoscopic procedures hence may pose significant risks of transmission (even for those not directly involving confirmed COVID-19 cases) as endoscopists and endoscopy staff are in close contact with patients during these aerosol generating procedures. This could result in inadvertent transmission of infection at time of endoscopy.

**Key Words:** Coronavirus; Endoscopy; Infection control; Personal protective equipment; Guidelines; Gastroenterology

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**Core Tip:** Coronavirus pandemic has united the world in taking enhanced measures in the endoscopy center to limit the spread of disease. However, considerable variation exists in the society recommendations that have come out of United States, Canada, Europe, United



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Kingdom, Australia, Asia and Japan. We summarize these recommendations, provide an overview, and describe our practical application of endoscopy in this challenging times.

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## INTRODUCTION

Numerous organizations and societies worldwide have come up with guidelines, recommendations or position statements to optimize the practice of endoscopy during the coronavirus disease 2019 (COVID-19) pandemic<sup>[1-9]</sup>. In addition, various centers have described their experiences regarding endoscopy in COVID-19<sup>[10,11]</sup>. The guidelines by leading organizations in the United States, Canada, Europe, United Kingdom, Australia, Asia and Japan are summarized in Table 1. We aim to compare practices regarding endoscopy during COVID-19 between countries and share our experience in devising and implementing infection prevention and control measures to mitigate risk of transmission during endoscopy.

## PRE ENDOSCOPY

### Procedure assessment and review

All organizations agree with the broad principle that elective cases should be individually assessed and reviewed, and elective non-urgent cases should be deferred. Depending on risk assessment, cases deemed to be of higher priority like those with suspected time-sensitive diagnosis *e.g.* malignancy should still proceed with endoscopic evaluation as delay may result in deleterious effect on patient outcomes. It is not a straightforward dichotomy, and the rationale underlying this approach is the need to balance medical urgency of procedure (as delay in procedure may have consequent delay in diagnosis and appropriate treatment, possibly leading to complications of disease or disease progression) with the risk of infection and utilization of potentially scarce resources. However, the definition of an elective case which should proceed differs considerably between various organizations and societies – it reflects that different areas have different incidences of COVID-19 and hence varying capacities for the performance of semi-urgent endoscopy. Our practice is that emergent cases are performed whereas outpatient elective cases are reviewed on a case-by-case basis and may be rescheduled. Direct-access endoscopy is suspended during this period.

Examples of emergent procedures which should be done: Upper or lower Gastrointestinal (GI) bleeding (BSG further recommends for upper GI bleeding to risk stratify to only for patients predicted to require endoscopic therapy, and for lower GI bleeding to limit to patients in whom interventional radiology is not possible or unsuccessful). Foreign body removal; Pancreatobiliary: Cholangitis; GI obstruction requiring palliation; Examples of elective procedures which should be deferred: Screening and surveillance oesophagogastrroduodenoscopy (OGD) or colonoscopy in asymptomatic patients. Evaluation of non-urgent symptoms. Therapeutic endoscopy in benign disease.

Of note, BSG recommends that if procedures are deferred for urgent referrals, the cases should be listed on a separate urgent deferred waiting list to ensure appropriate follow-up and to prioritize endoscopy when normal activities resume.

Our experience is also that there are many patients who do not fit clearly into either emergent or elective categories, for example, patients with symptomatic iron-deficiency anemia who are not actively bleeding, but for whom delay until normal endoscopic services resume might be life threatening or have prognostic implications due to undiagnosed peptic ulcer disease or GI malignancy. After clinical review, numerous such patients would still be considered to proceed with endoscopy. Despite utilizing this approach, we have reduced the total endoscopy case load to less than

Table 1 Comparison of guidelines / recommendations / position statements

	United States Joint GI Society	United States (AGA)	United States (ASGE)	Canada (CAG)	Europe (ESGE/ESGENA)	United Kingdom (BSG/JAG)	Australia (GESA)	Asia (APSDE)	Japan (JGES)
Pre-endoscopy									
Procedure review and stratification	Urgent: Perform, non-urgent which may need to be performed, non-urgent: Postpone	Time-sensitive (within 24 h-8 wk), not time-sensitive; - defer procedure on case-by-case basis	Urgent/emergent: Perform, elective: Postpone	Essential: Perform, not essential: Postpone	Emergent, elective: Postpone; Evaluate risk of GI disease-related <i>vs</i> COVID-19 related morbidity and mortality	Emergent/essential (continue), needs discussion (case-by-case basis), defer until further notice	Urgent/emergent: Perform, semi-elective: Review, elective: Postpone	Urgent: Perform, semi-urgent: Case-by-case basis, elective: Postpone	
Procedures to proceed		Upper GI bleeding; Lower GI bleeding (if SARS-CoV-2 PCR negative)	Upper/lower GI bleeding; Dysphagia causing decreased intake; Time-sensitive diagnosis <i>e.g.</i> evaluation/treatment of cancer/pre; Cancerous conditions; IBD if endoscopy may change management; GI obstruction requiring palliation; Cholangitis	GI bleeding which is life-threatening; GI obstruction ( <i>e.g.</i> esophageal obstruction due to food bolus / foreign body); Cholangitis	Upper/lower GI bleeding with haemodynamic instability; Foreign body in esophagus or high-risk foreign body in stomach; Obstructive jaundice; Cholangitis	Upper GI bleeding likely to require therapy; Lower GI bleeding which failed radiological intervention; Foreign body; GI obstruction requiring stenting; Cholangitis, infected peri-pancreatic collection; Nutrition support: Urgent NJT/PEG	Upper GI bleeding, clinically significant; Lower GI bleeding not due to haemorrhoids; Evaluation/treatment of cancer; New diagnosis / flare of IBD in which endoscopy may change management; GI obstruction; Cholangitis, infected/symptomatic peri-pancreatic collection; Nutrition: Urgent NGT/NJT/PEG	GI bleeding; Foreign body; GI obstruction requiring stenting; Management of leakage/perforations; Biliary sepsis; Nutrition: Urgent GI access for feeding	
Procedures to consider (case-by-case)	Evaluation of suspected cancer; Evaluation of significant symptoms	Conditions in which delay in diagnosis can have implications on treatment ( <i>e.g.</i> cancer, IBD); Treatment of pre-cancerous lesions <i>e.g.</i> high-grade dysplasia in Barrett's, EMR of large colon polyp	Mild dysphagia; Iron deficiency anaemia		High priority; Upper GI bleeding without instability; Severe anaemia; Dysphagia / dyspepsia with alarm symptoms; Evaluation of suspected cancer <i>e.g.</i> imaging evidence of mass; Treatment of early cancer/pre-cancerous lesions; Pancreatobiliary stent replacement; Low priority; Iron deficiency anaemia; Pancreatic cyst (depends on risk features)	Variceal surveillance in high risk cases ( <i>e.g.</i> recent acute bleeding); Evaluation of malignant conditions; EUS for staging/planning of treatment of cancer; Treatment of high-risk lesions <i>e.g.</i> EMR/ESD	Dysphagia; Iron deficiency anaemia (except female < 50 yr) where no other likely cause on clinical exam; Marked weight loss; Evaluation of suspected cancer <i>e.g.</i> abnormal imaging; Treatment of pre-cancerous lesions <i>e.g.</i> resection of large colonic polyp; Pancreatobiliary stent replacement/removal	High suspicion of cancer; Treatment of cancer/pre-cancerous lesions with EMR/ESD; ERCP for hepatobiliary cancers	
Procedures to defer		Screening / surveillance colonoscopy	Screening / surveillance OGD or colonoscopy in asymptomatic patients (including variceal surveillance);	Screening / surveillance OGD or colonoscopy	Screening / surveillance; Evaluation of dyspepsia, reflux or IBS-like symptoms with no alarm symptoms	Screening / surveillance; Assessment of disease in IBD; Low-risk follow-up scopes ( <i>e.g.</i> esophagitis or gastric	Screening / surveillance; Non-specific symptoms; Evaluation of GERD, probable IBS; EUS for pancreatic cyst (low risk)/chronic	Screening / surveillance; Diagnostic; Therapeutic for benign disease	

			Evaluation of non-urgent symptoms or disease states (e.g. intermediate risk pancreatic cysts)			ulcer healing); EUS for biliary dilatation, possible stones, pancreatic cyst (not high risk)	pancreatitis; Asymptomatic gallstones		
Postpone non-urgent procedure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patient pre-screening	Screen for fever, respiratory symptoms and high risk exposure				Screen for symptoms (fever, cough, shortness of breath, diarrhea) and contact history		Screen for symptoms (flu-like symptoms), contact and travel history	Screen for fever, contact history, travel history, occupational exposure	Screen for fever, symptoms (respiratory tract infection symptoms, shortness of breath, diarrhea, dysosmia/dysgeusia, fatigue), contact and travel history
Patient assessment	Check patient's temperature on arrival				Check patient's temperature on arrival				Check patient's temperature on arrival
Patient precautions	Ensure patients maintain an appropriate distance (at least 6 ft) from each other				Patients should use face masks and maintain a distance (at least 1-2 m)			Ensure patients maintain an appropriate distance (2 m) from each other	Ensure patients maintain an appropriate distance from each other
Endoscopy staff screening					Daily assessment of symptoms/signs and risk factors; Isolation and testing if symptomatic				Daily assessment of symptoms/signs and risk factors
Waiting area policy	Avoid bringing patients (or escorts) ≥ 65 or with 1 of the CDC recognised risks				No caregiver/relatives allowed except in special situations			No caregiver/relatives allowed except in special situations	
During Endoscopy									
Type of PPE	Mask (type not specified), eye shield/goggles, face shield, gown, gloves	N95 mask (or PAPR), double gloves	N95 mask	High risk (include all upper GI procedures): N95 mask or equivalent, double gloves; Low risk: Surgical mask, gloves; Common: Goggles/face shield, water-proof gown, shoe covers, hairnet	Confirmed COVID-19 or high risk cases: N95 mask or equivalent, double gloves; Low risk: Surgical mask, gloves; Common: Goggles/face shield, water-proof gown, shoe covers, hairnet	Confirmed COVID-19 or high-risk (upper GI procedures): FFP3 mask, full visor, long-sleeved gown; Low risk: Surgical mask, glasses/visor, disposable apron; Common: Gloves, shoe covers, hairnet	Confirmed/suspected COVID-19 or high risk cases: N95 mask (or FFP2/3); Low risk: Surgical mask; Common: Goggles/face shield, long-sleeved waterproof gown, gloves	Confirmed/suspected COVID-19 cases: N95 mask; Low risk: N95 or surgical mask; Common: Goggles/face shield, water-resistant gown, gloves	Face mask, goggle/face shield, long-sleeved gown, gloves, cap

hairnet						
Members of endoscopy team	Only essential staff should be present in procedures	Minimise number of staff in room during endotracheal intubation (anaesthesia team only); avoid switch in staff during procedures	Only essential staff should be present in procedures	Restrict number of staff in procedures	Confirmed/ at high risk of COVID-19 cases: Restrict number of staff in procedures; Low risk: Standard number of staff	1 experienced endoscopist + 2 nurses only
Endoscopy training		Review appropriateness of trainee involvement in procedures	Modify training - encourage use of e-learning	Limit trainee involvement	Confirmed/ at high risk of COVID-19 cases: No trainees; Low risk: Trainees can be involved	
Location	Confirmed/suspected COVID-19 cases: Do procedure in negative pressure rooms	Confirmed/suspected COVID-19 cases: Do procedure in negative pressure rooms	Confirmed/high-risk of COVID-19 cases: Do procedure in negative pressure rooms		Confirmed/high risk of COVID-19 cases: Do procedure in negative pressure rooms	Confirmed/suspected COVID-19 cases: Do procedure in negative pressure rooms
Post-Endoscopy						
Follow-up	Consider phone follow-up at 7 and 14 d to ask about new diagnosis or development of symptoms of COVID-19		Consider contacting patients at 7 and 14 d to ask about new diagnosis or development of symptoms of COVID-19			

APSE: Asian Pacific Society for Digestive Endoscopy; COVID-19: Coronavirus disease 2019; PAPR: Powered air-purifying respirators; IBD: Inflammatory bowel disease; OGD: Oesophagogastroduodenoscopy; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; GI: Gastrointestinal; EUS: Endoscopic ultrasonography.

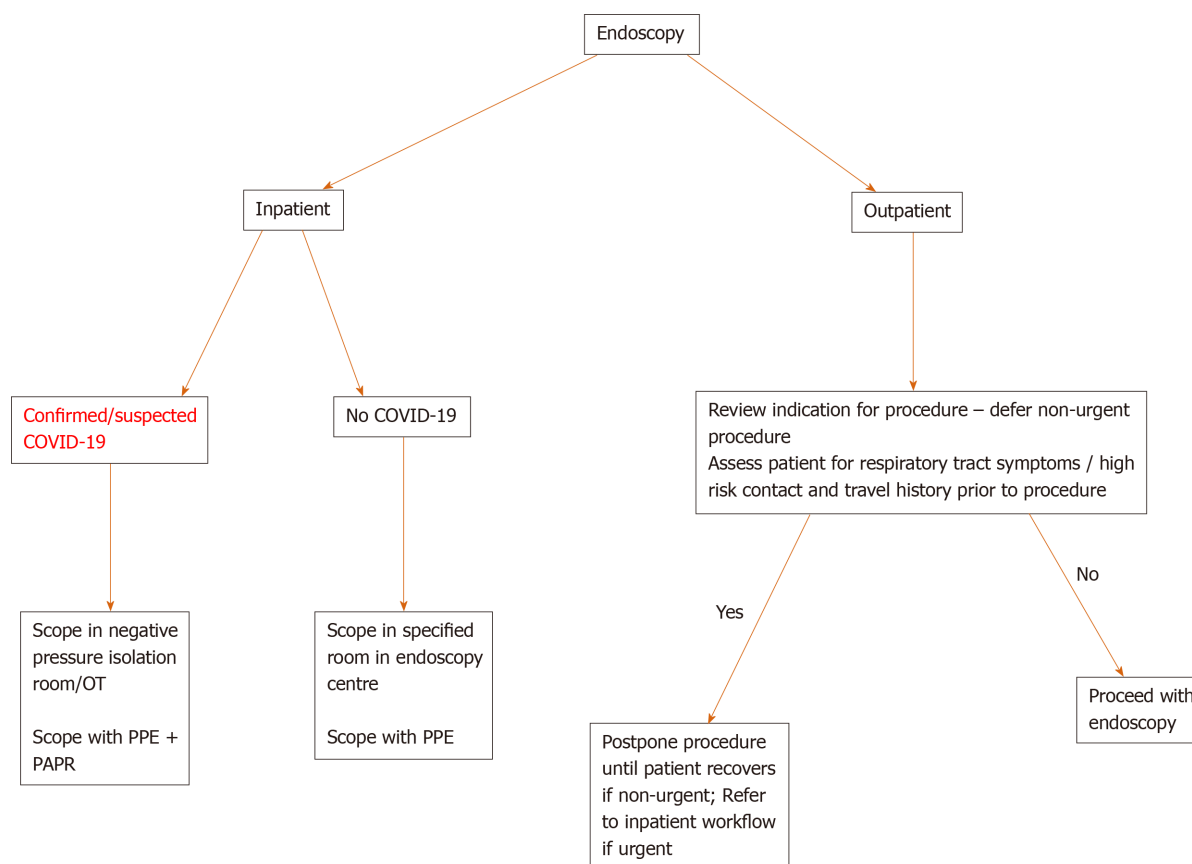
40% of the usual load in our center.

### **Patient assessment and screening**

At our center, prior to endoscopy, patients are pre-screened for symptoms (fever, upper respiratory tract symptoms) and significant contact and travel history.

On arrival at the endoscopy center, patients are screened again for symptoms, and patients' temperatures are checked. After passing through screening and temperature taking, patients will enter the waiting area. All patients should be wearing at least a surgical mask and should maintain adequate physical distance of 1-2 m from others. Asian Pacific Society for Digestive Endoscopy and ESGE suggest that no caregivers or relatives should be allowed to enter the endoscopy center.

We have devised a simple algorithm to aid decision making regarding timing of procedures ([Figure 1](#)).



**Figure 1 Workflow for endoscopy during coronavirus disease 2019.** Personal protection equipment: N95 mask, eye protection (goggles), long-sleeved waterproof gown, one set of gloves.

## DURING ENDOSCOPY

### *Personal protection equipment*

All organizations concur that for all procedures, all members of the endoscopy team should wear appropriate personal protection equipment (PPE) – usually consisting of N95 or surgical mask, eye shield/goggles, face shield, water-resistant gown and gloves. AGA and ASGE advise the use of N95 mask for all procedures. In contrast, ESGE, CAG and GESA limit the use of N95 mask for high-risk procedures only. AGA also specifies that 2 sets of gloves (rather than 1 set) should be used in all procedures, whereas CAG and ESGE suggest that 2 sets of gloves be used in high-risk procedures only. This minimizes contamination by reducing risk of transferring viral organisms from PPE to clothes or the rest of the body during removal of PPE. These differences probably reflect variable availability and practical rationing to conserve limited PPE resources amidst competing needs. Endoscopy staff should be trained in donning and removing PPE, and hand hygiene practices must be observed strictly.

In our center, we have enhanced our universal precautions, to N95 mask, eye goggles, water resistant gown and gloves for endoscopy in all patients. In addition, for confirmed or suspected COVID-19 cases, the endoscopist and assisting nurses wear all PPE with the addition of powered air-purifying respirators (PAPR) as an additional barrier. All confirmed or suspected COVID-19 cases should have been admitted to hospital. Suspected cases are defined as per guidance from our Ministry of Health<sup>[12]</sup> – usually suspected if they have clinical signs and symptoms suggestive of acute respiratory illness, and COVID-19 cases are confirmed with syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test of respiratory or nasopharyngeal swabs.

### *Members of endoscopy team*

In our center, endoscopy staff are assessed daily for symptoms and signs suggestive of COVID-19 infection – temperature is checked twice a day. Staff are grouped into teams of 2-3 which are segregated into separate endoscopy rooms and remain together for the whole day. This is to minimize concomitant exposure to infection and prevent potential spread of infection between teams.

The number of endoscopy staff should be curbed with only essential staff (senior endoscopist +/- trainee, maximum of 2-3 assisting nurses) allowed in the room during procedures. Particular mention should be made of different perspectives of the involvement of trainees in procedures. AGA and BSG have recommended to review and consider limiting their participation in procedures in view of constraints in PPE supply and concerns of increased procedural time. GESA has adopted a more nuanced approach and suggested that trainees should be restricted from participating in procedures involving confirmed COVID-19 cases or cases at high risk of COVID-19 but should be allowed to do procedures involving cases at low risk of COVID-19. Our center adopts this stance, valuing trainee participation in standard endoscopy but limiting their exposure to COVID-19 confirmed or suspected cases.

### ***Procedure logistics***

In our center, for confirmed or suspected patients with COVID-19, endoscopic procedures should be done in negative pressure rooms if fluoroscopy is not required, or in a designated operating theatre with negative pressure if fluoroscopy is required. In limited resource settings where negative pressure rooms are not available, AGA advises portable industrial-grade high-efficiency particulate air filters as an alternative, in line with Centers for Disease Control and Prevention guidelines. Our center has a total of 6 available endoscopy rooms-all inpatient cases are consolidated in 1-2 specified rooms, and outpatient cases are done in other available rooms. This ensures no cross-contamination between patients.

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## **POST ENDOSCOPY**

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### ***Cleaning and disinfection***

Standard cleaning and disinfection of endoscopy rooms and endoscopy equipment should continue. Endoscopes and endoscopic accessories are reprocessed with standardized reprocessing procedures. Our center's practice is in line with the United States multi-society guidelines<sup>[13]</sup>. Endoscopes are cleaned manually-endoscope components are disassembled, and endoscope and their components are immersed in detergent which is compatible with the endoscope. All available channels are flushed and brushed to remove any residue. Endoscopes and their components are subsequently subjected to high-level disinfection with an automated endoscope reprocessing unit.

For confirmed or suspected COVID-19 cases, used endoscopes and endoscopic equipment will be cleaned on site with disinfectant. Used scopes will then be placed in biohazard bags (double bagged) into a container and transported back to the endoscopy centre for further cleaning and reprocessing, which will be done separately from other endoscopic equipment.

All endoscopy staff involved in disinfection and reprocessing of endoscopes and endoscopic equipment should be wearing PPE.

### ***Follow-up***

Patients can be contacted at 7-d and 14-d post-procedure to ask about new diagnosis of COVID-19 or development of symptoms of COVID-19 infection. This is suggested by the United States Joint GI Society and ESGE but not routinely practiced elsewhere. Our center conducts routine follow-up calls as per our patient feedback process but not specifically for COVID-19.

We have formulated a proposed workflow incorporating the above measures which can enhance safety of endoscopy in this period (Table 2).

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## **RESUMING ENDOSCOPY AFTER CORONAVIRUS DISEASE PANDEMIC**

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With numerous countries employing strategies such as social distancing to decrease rates of SARS-CoV-2 infection, the peak of the COVID-19 pandemic may have passed and attention now turns to how best to re-introduce normal activities and services safely. AGA and Digestive Health Physicians Association (DHPA), ASGE, and BSG have recently published guidelines on resumption of endoscopy during the COVID-19 pandemic<sup>[14-16]</sup>. Timing of resuming elective procedures should be guided by incidence of COVID-19 cases in the local community, and availability of equipment and manpower. AGA/DHPA propose to resume elective endoscopic procedures when

**Table 2 Infection control measures in the endoscopy unit**

Issues	Steps
Pre-procedure	
Risk assessment; Patient/ Procedure; Patient precautions	Inpatient urgent cases are done on a case-to-case basis; Outpatient elective non-urgent cases are reviewed by physician in charge – proceed with cases with suspected significant or time-specific diagnosis, reschedule all other cases; Direct access endoscopy is suspended; Prior to endoscopy: Pre-screen patients for history of fever or upper respiratory tract symptoms (cough, sore throat, rhinorrhea), significant contact and travel history, or if they have been issued a home quarantine order or stay home notice; This includes patients who have family members or close contact with suspected or confirmed COVID-19 case, and patients with recent travel to high risk countries in the past 14 d. On day of endoscopy: Check patient's body temperature on arrival and ensure patients are at least 2 m apart in the endoscopy centre. All patients and staff wear surgical masks while in the endoscopy centre. Hand hygiene is performed before and after patient contact; Only 1 visitor per patient will be allowed to enter the endoscopy centre.
Procedure	
Personal protection equipment (PPE)	All members of the endoscopy team wear PPE consisting of N95 mask, face shield, eye shield/goggles, long-sleeved surgical gown and gloves; For confirmed COVID-19 cases; The transfer team will wear PPE while transporting patients to and from the ward; The endoscopist and assisting nurses will wear PPE with powered air-purifying respirators (PAPR) (eye shield/goggles are not required with a PAPR) before entering the room; All endoscopy staff are trained to don and remove PPE accurately; Hand hygiene is performed before wearing and after removing PPE. Wearing of PPE follows these steps: Gown is worn first, followed by N95 mask and eye shield/goggles, then face shield, and finally gloves. Removal of PPE follows these steps: Remove gloves and gown first inside the room, then remove PAPR and N95 mask outside the room or in ante-room (if available).
Members of endoscopy team	Endoscopy staff are grouped into teams and segregated into separate endoscopy rooms. Endoscopy staff are advised to minimise personal contact and interaction with staff from other groups.
Logistics	For confirmed or suspected patients with COVID-19, endoscopic procedures are done in negative pressure rooms. If fluoroscopy is not required, endoscopy is done at bedside in negative pressure isolation room in the ward. If fluoroscopy is required, endoscopy is done in a designated major operating theatre room. The endoscopy team prepares all necessary equipment and scopes on a clean trolley before proceeding to the location. All other inpatient cases are consolidated in a specified room in the endoscopy centre. If this is not possible, the inpatient case will be scheduled as last case in the room. Outpatient elective cases are performed in other available rooms.
Post procedure	
Cleaning and disinfection	Standard cleaning and disinfection of endoscopy rooms continue. All surfaces in endoscopy rooms are cleaned, followed by disinfection. For confirmed COVID-19 cases. Used equipment will be wiped down on site with disinfectant, placed in a labeled "dirty" trolley and brought back to endoscopy centre for further cleaning and disinfection. Used scopes will be wiped down on site with disinfectant, placed in a biohazard bag (double bagged), and placed in a rigid container with lid for transportation back to the endoscopy centre for reprocessing.

PPE: Personal protection equipment; COVID-19: Coronavirus disease 2019; PAPR: Powered air-purifying respirators; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

there is a sustained decrease in rate of new COVID-19 cases in the community for at least 14 d, and the decision to resume should also take into consideration availability of resources required to ensure the safety of both healthcare staff and patients.

Resumption of elective endoscopic procedures should be done cautiously and gradually in a phased manner. Both AGA/DHPA and ASGE recommend additional measures for pre-procedure patient screening. AGA/DHPA suggest conducting SARS-CoV-2 PCR testing within 48 h before procedure; if unable to do so, to consider asking patients to keep daily temperature logs for 10 d before procedure. On the day of procedure, a symptom questionnaire will be administered to patients and their temperatures will be checked. ASGE suggests doing pre-screening with a questionnaire on symptoms, contact history, travel history, and occupational exposure within 72 h before procedure. Responses to the questionnaire should be updated on the day of procedure. The rest of the infection prevention and control measures



discussed above should continue to be implemented and observed. Additionally, ASGE mentions that patients should be followed up and surveyed 1-2 wk post-procedure – they are advised to inform the endoscopy centre if they develop symptoms or are diagnosed with COVID-19 within 14 d of procedure.

## CONCLUSION

The COVID-19 pandemic has united the world in taking enhanced measures in endoscopy to limit the spread of disease. However, different approaches to these measures highlight system differences in approach to care and logistic limitations. Guidelines and recommendations on endoscopy during COVID-19 are not exhaustive and not inflexible. Of note, many of these guidelines were released consecutively as the pandemic evolved in individual countries and might not necessarily reflect the current state of practice. In these challenging and rapidly evolving times, there is constant emergence of new information, and new innovations in testing and treatment. We should hence be prepared to continually adapt our practices to improve quality and safety of endoscopy during the pandemic.

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Retrospective Study

## Comparison of the reverse bevel versus Franseen type endoscopic ultrasound needle

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**Institutional review board**

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### Abstract

#### BACKGROUND

Reverse bevel (RB) needle is widely used for endoscopic ultrasound fine needle biopsy (EUS-FNB). A 3-plane symmetrical needle with Franseen geometry (FG) has recently become available.

#### AIM

To compare the clinical efficacy of FG to that of RB needle.

#### METHODS

A retrospective cohort study of all adult patients who underwent EUS-FNB for solid and mixed lesions either with 22G RB needle or 22G FG needle between January 2016 and February 2019 was undertaken. All cytology slides were reviewed by an independent gastrointestinal cytopathologist blinded to the needle used and the initial cytology report. The primary and secondary outcomes were to assess the sample adequacy using Euro-cytology criteria and the number

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of cell clusters, respectively.

## RESULTS

Two hundred and twenty six procedures were included in the study. RB needle was used in 128 procedures and FG needle in 98 procedures. The baseline characteristics of both groups were comparable. On multivariable analysis, FG needle ( $P = 0.02$ ) and location of the lesion ( $P < 0.01$ ) were independently associated with adequate tissue. Further, the use of FG needle ( $P = 0.04$ ) and the size of the lesion ( $P = 0.02$ ) were independently associated with acquisition of increased number of cell clusters.

## CONCLUSION

FG needle is superior to RB needle in acquiring adequate tissue and attaining higher number of cell clusters for solid and mixed lesions.

**Key Words:** Endoscopic ultrasound; Fine needle aspiration; Fine needle biopsy; Reverse bevel; Franseen geometry; Tissue acquisition

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**Core Tip:** Despite retrospective, it is the first paper to try to compare the performance of reverse bevel fine needle biopsy (FNB) needle with Franseen geometry FNB needle in term of tissue acquisition and number of cell groups in specimen. Slides reviewed by an independent expert gastrointestinal cytopathologist blinded to needle type used and original cytology reports to minimize bias.

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## INTRODUCTION

Endoscopic ultrasound (EUS) is widely used as a diagnostic tool to obtain tissue from abdominal and thoracic lesions *via* the gastrointestinal (GI) tract. The procedure is minimally-invasive and well-tolerated by patients<sup>[1,2]</sup>. A number of factors have been shown to influence successful tissue acquisition including lesion position<sup>[3,4]</sup>, lesion size<sup>[5-8]</sup>, needle type<sup>[9-12]</sup>, needle size<sup>[13-16]</sup>, number of passes<sup>[17-21]</sup>, technical skills<sup>[22-25]</sup> and the presence of rapid on-site cytological evaluation (ROSE)<sup>[1,26-28]</sup>.

Fine needle biopsy (FNB) needles have been in use since 2003<sup>[29]</sup>. European Society of Gastroenterology recommends using 22G or 25G needles for the sampling of solid masses and lymph nodes<sup>[1]</sup>. Reverse bevel (RB) needle (ProCore®, Cook Medical) is the most widely studied FNB needle<sup>[13,15,17,30-41]</sup>. Evidence for needles such as Franseen geometry (FG) needle (Acquire™, Boston Scientific), fork-tip needle (Shark Core; Medtronic) and antegrade core trap needle (ProCore® 20G, Cook Medical) are emerging, but limited. Two meta-analysis comparing RB needle with fine needle aspiration (FNA) needle reported no significant difference in sample adequacy, diagnostic accuracy or core tissue acquisition rate; however, RB needle was able to establish the diagnosis with less number of passes<sup>[30,31]</sup>.

On the other hand, in recent studies, FG needle has been shown to have a better tissue acquisition, better tissue architecture, higher diagnostic accuracy compared to standard FNA needle<sup>[42-44]</sup>. Studies have also shown better performance of FG needle against other newer needles such as Echo-Tip Ultra needle (Cook Medical, Indiana)<sup>[45]</sup> and antegrade core trap needle (ProCore® 20G, Cook Medical)<sup>[46]</sup>. However, the literature on direct comparison of FG needle with the commonly used RB needle is lacking. In this retrospective study, we compare the real-life efficacy of 22G FG needle to that of 22G RB needle.

## MATERIALS AND METHODS

### **Patient selection and data collection**

A single centre retrospective cohort study was undertaken at Nottingham University Hospitals NHS Trust, a high-volume regional referral centre. All adult (age  $\geq 18$  years) patients who underwent EUS-FNB between January 2016 and February 2019, using either 22G RB needle or 22G FG needle were included in this study. Those who underwent EUS-FNB with other types of needles and 25G FG were excluded due to small numbers. Demographic characteristics, details of EUS procedure and cytopathology reports were extracted from the electronic patient record and endoscopy database.

The study was approved by Nottingham University Hospitals National Health Service Trust review board (ID number 19-551C).

### **Endoscopic ultrasound and tissue acquisition**

All procedures were carried out under conscious sedation or deep sedation with general anaesthesia using either Olympus GF-UCT240 or Olympus GF-UCT260 curvilinear-array echo-endoscope. Fanning technique with dry suction or slow pull through was used for tissue acquisition. The specimens were collected in either Cytorich preservative fluid or formalin, and then sent to pathology department for processing and reporting. ROSE of specimens was not performed in any of the procedures as it was not available. For the purposes of this study, location of the lesion was categorised into four groups—gut wall lesions, pancreatic lesions, extramural lesions and lymph nodes. The nature of lesion was categorised into solid or mixed (solid with cystic component).

### **Blinded review of cytology slides**

All cytology slides were reviewed by an independent expert GI cytopathologist (Haider SA), who was blinded to the type of needle used and previous cytology report, and reported according to the Euro-cytology criteria<sup>[46]</sup> (C1: Inadequate and non-diagnostic; C2: Benign; C3: Atypical cells found which favour benign; C4: Suspicious of malignancy; C5: Malignant). For the purpose of assessing tissue adequacy, C1 category was defined as inadequate tissue acquisition; C2, C3, C4, and C5 categories were defined as adequate tissue acquisition. The number of cell clusters per slide was also reported by the cytopathologist. A cell cluster was defined as group of cells with more than 2 cells; individual scattered cells were not counted as cell clusters. Cell cluster data was divided into greater than or equal to 50 cell clusters and less than 50 cell clusters for analysis.

### **Outcomes**

The primary outcome was to identify factors that impact tissue adequacy (Euro-cytology C1 *vs* C2-C5) and the secondary outcome was to identify factors that impact the number of cell clusters in the specimen slides.

### **Statistical analysis**

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as number and percentage. All statistical analyses were performed using SPSS for Windows v26 (IBM Corp, Armonk, NY, United States). Fisher's exact test was used for categorical parameters with  $2 \times 2$  contingency table and Pearson's chi-square test was used for categorical parameters with contingency table dimensions that exceeded  $2 \times 2$ . Unpaired student's *t* test or 1-way ANOVA test was used to study the relationship between categorical parameters with continuous parametric parameters. A *P* value of  $< 0.05$  was considered significant. Variables with a *P* value  $\leq 0.10$  were included in the multivariable logistic regression analysis to identify independent factors. Cohen's kappa test was used to measure the inter-rater agreement between the interpretation of the independent GI cytopathologist and the original cytology reports.

## RESULTS

### **Demographics and clinical characteristics**

A total of 226 patient episodes were included in this study. Of which, 128 procedures were sampled using 22G RB needle and 98 were sampled using 22G FG needle. The



demographic characteristics of RB and FG needle groups were comparable and summarised in [Table 1](#). There were no differences in age ( $P = 0.29$ ), gender distribution ( $P = 0.42$ ), location of the lesion ( $P = 0.55$ ), nature of the lesion ( $P = 0.34$ ), size of the lesion ( $P = 0.67$ ), number of needle passes ( $P = 0.77$ ), presence of trainee ( $P = 0.12$ ) and the use of Sonovue contrast ( $P = 0.17$ ) between the two groups.

### Assessment by a GI cytopathologist

The kappa score of agreement between the independent GI cytopathologist review and the original cytology results was 0.671 (95%CI: 0.595-0.747;  $P < 0.01$ ).

### Primary outcome

The overall sample adequacy of the entire study cohort was 87.6%. The tissue adequacy in the FG needle group was 93% and RB needle group was 83%.

On univariable analysis, use of FG needle ( $P = 0.03$ ) and the location of lesion ( $P < 0.01$ ) were associated with adequate tissue acquisition ([Table 2](#)). Age ( $P = 0.88$ ), gender ( $P = 1.00$ ), presence of trainee ( $P = 1.00$ ), lesion size ( $P = 0.11$ ), nature of lesion ( $P = 0.62$ ), number of passes ( $P = 0.61$ ) and Sonovue contrast ( $P = 0.50$ ) were not associated with adequate tissue acquisition ([Table 2](#)). On binary logistic regression analysis, the use of FG needle (OR 3.01; 95%CI: 1.15-7.86,  $P = 0.02$ ) and the location of the lesion with pancreas (OR 9.42; 95%CI: 3.51-25.33,  $P < 0.01$ ) were independently associated with adequate tissue acquisition ([Table 2](#)).

### Secondary outcome

On univariable analysis, only the lesion size ( $P = 0.02$ ) was associated with acquisition of  $\geq 50$  cell clusters; use of FG needle ( $P = 0.07$ ) and solid lesions ( $P = 0.09$ ) approached, but did not reach statistical significance ([Table 3](#)). Age ( $P = 0.67$ ), gender ( $P = 0.13$ ), location of the lesion ( $P = 0.39$ ), presence of trainee ( $P = 0.25$ ), number of passes ( $P = 0.65$ ) and Sonovue contrast ( $P = 1.00$ ) were not associated with acquisition of  $\geq 50$  cell clusters ([Table 3](#)). Lesion size, type of needle and nature of the lesion were included in the binary logistic regression analysis. Use of FG needle (OR 1.79; 95%CI: 1.02-3.12,  $P = 0.04$ ) and larger lesion size (OR 1.02; 95%CI: 1.00-1.03,  $P = 0.02$ ) were independently associated with acquisition of  $\geq 50$  cell clusters ([Table 3](#)).

## DISCUSSION

This is the first study to report on the comparative performance of 22G FG needle and 22G RB needle in acquiring adequate tissue after blinded assessment. There was good correlation between the independent cytopathological review and original report. The location of the lesion and the use of FG needle were independent predictors of improved tissue adequacy; however, the latter was the only modifiable variable in this study that could improve tissue acquisition.

The superior performance of FG needle is likely due to its three plane (Franseen geometry) cutting tip which may have enhanced tissue acquisition. A prospective study comparing FG needle and FNA needle reported that the FG needle performed significantly better compared to FNA needle for median area of total tissue and cell block diagnostic yield<sup>[47]</sup>. However, the study did not report an independent association between FG needle and improved sample adequacy.

Lesion location was also independently associated with improved sample adequacy. This finding is in line with a retrospective study analysing EUS-guided Trucut biopsy from 247 patients which reported that the site of biopsy was an independent predictor of diagnostic yield<sup>[3]</sup>.

In addition to Euro-cytology classification, we also assessed the number of cell clusters as an indirect marker of tissue acquisition. Larger lesions and the use of FG FNB needle were significantly associated with  $\geq 50$  cell clusters in the specimens. Bethesda system of classification for thyroid nodule FNA specimens suggests that there should be at least 6 cell clusters with each cluster having at least 10 representative cells for the sample to be deemed adequate<sup>[48]</sup>. However, no such requirement exists for GI and pancreatic lesions to assess sample adequacy. Based on cytopathologist review, 50 or more cell clusters with at least two cells in each cluster was chosen as the most reliable alternate indicator of tissue adequacy. We speculate that 50 or more cell clusters with at least 2 cells in each cluster would enable the cytopathologist to make a diagnosis with high confidence in distinguishing benign from malignant lesions. This, however, needs further evaluation and validation in future studies.

**Table 1** Baseline characteristics of patients included in this study (*n* = 226)

Baseline characteristic	22G RB needle ( <i>n</i> = 128)	22G FG needle ( <i>n</i> = 98)	<i>P</i> value
	<i>n</i> (%) or (mean ± SD)	<i>n</i> (%) or (mean ± SD)	
Location of lesion			
Gut wall lesions <sup>1</sup>	17 (13)	13 (13.3)	0.55
Pancreatic lesions	65 (51)	58 (59.2)	
Lymph node	23 (18)	15 (15.3)	
Extramural lesions <sup>2</sup>	23 (18)	12 (12.2)	
Lesion nature			
Solid	124 (97)	92 (94)	0.34
Mixed	4 (3)	6 (6)	
Lesion size (mm)	35.0 (20.9)	36.0 (16.0)	0.67
Age (year)	66.3 (12.4)	68.1 (11.6)	0.29
Gender			
Female	58 (45)	39 (40)	0.42
Male	70 (55)	59 (60)	
Presence of trainee			
Yes	39 (30)	40 (41)	0.12
No	89 (70)	58 (59)	
Number of passes	3.1 (0.8)	3.2 (0.7)	0.77
Contrast sonovue			
Yes	1 (1)	4 (4)	0.17
No	127 (99)	94 (96)	

<sup>1</sup>Gut wall lesions include oesophageal, gastric, duodenal or rectal wall lesions.

<sup>2</sup>Extramural lesions-does not include pancreatic lesions and lymph node. RB: Reverse bevel; FG: Franseen geometry.

The independent association between lesion size and higher number of cell clusters corroborates previous study findings. A retrospective study on 583 patients reported a strong correlation between diagnostic yield and the size of the lesion<sup>[5]</sup>. Another retrospective study involving 271 patients reported that the size of the lesion was an independent factor for tissue acquisition<sup>[8]</sup>. These indicate that care is needed with smaller lesions and the type of needle used, a modifiable factor, become even more important in smaller lesions.

Three passes is being considered sufficient when using 22G for tissue acquisition. Three or more number of passes with FNA needle has been shown to have a satisfactory sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 84.3%, 97%, 99%, 64%, and 84%, respectively<sup>[21]</sup>. Given that the FNB needle requires significantly lower passes for adequate tissue acquisition<sup>[18]</sup>, it is not unreasonable to speculate that the number of passes made in this study was more than adequate for tissue acquisition in both needle groups (mean > 3 in both FG and RB needle groups), and therefore could be the reason why it was not an independent predictor of adequate tissue acquisition. This is further supported by a previous retrospective study which showed adequate yield of histological material with lower number of passes<sup>[45]</sup>.

A randomized control trial (RCT) comparing FG needle and fork tip needle reported a diagnostic cell block yield of 92% and 96%, respectively with no statistical significance between the two needles<sup>[49]</sup>. Another RCT comparing FG and FNA needles reported a diagnostic cell block yield of 97.8% for FG needle<sup>[42]</sup>. An observational study comparing 20G forward bevel needle and 22G FG needle found no difference in histological diagnosis rate, but FG needle achieved longer mean cumulative length of tissue core biopsies per needle pass<sup>[50]</sup>. A prospective study comparing FG needle with standard FNA (expect, Boston scientific) needle reported increased rate of tissue



**Table 2 Factors associated with tissue adequacy-univariable and multivariable logistic regression analysis**

Factors	Univariable analysis			Multivariable analysis	
	Insufficient tissue (C1) (n = 29)	Sufficient tissue (C2-C5) (n = 197)	P value	OR (95%CI)	P value
	n (%) or (mean $\pm$ SD)	n (%) or (mean $\pm$ SD)			
FNB needle used <sup>a</sup>					
22G RB needle	22 (76)	106 (59)	0.03	3.01 (1.15-7.86)	0.02
22G FG needle	7 (24)	91 (41)			
Gender					
Female	12 (41)	85 (43)	1.00		
Male	17 (59)	112 (57)			
Age (years)	66.7 (16.4)	67.2 (11.4)	0.88		
Presence of trainee					
Yes	7 (24)	72 (37)	0.22		
No	22 (76)	125 (63)			
Location of lesion <sup>a</sup>					
Gut wall lesions <sup>1</sup>	6 (20)	24 (12)	< 0.01	2.64 (0.85-8.19)	0.09
Pancreatic lesions	8 (28)	115 (58)		9.42 (3.51-25.33)	< 0.01
Lymph node	15 (52)	23 (12)		1.18 (0.00-669.44)	0.99
Extramural lesions <sup>2</sup>	0 (0)	35 (18)		1.00	
Lesion size (mm)	30.1 (20.4)	36.2 (18.6)	0.11		
Lesion nature					
Solid	27 (94)	189 (96)	0.62		
Mixed	2 (6)	8 (4)			
Number of passes made	3.1 (0.7)	3.1 (0.8)	0.61		
Sonovue contrast					
Yes	1 (97)	4 (2)	0.50		
No	28 (3)	193 (98)			

<sup>a</sup>Parameters with a  $P < 0.10$  on univariable analysis were included in the multivariable analysis and these parameters are indicated by an asterisk.

<sup>1</sup>Gut wall lesions include oesophageal, gastric, duodenal or rectal wall lesions.

<sup>2</sup>Extramural lesions do not include pancreatic lesions and lymph node. Tissue adequacy: C1: Insufficient; C2: Benign; C3: Atypical; C4: Suspicious; C5: Malignant. FNB: Fine needle biopsy; RB: Reverse bevel; FG: Franseen geometry.

acquisition with FG needle<sup>[43]</sup>. In par with previous literature, the cytological yield of FG needle in our study was 93%. Such high tissue yield with newer needles is likely ameliorate the need for ROSE in the future.

A major limitation of this study is its retrospective nature and the potential for inherent selection bias. It was difficult to ascertain if a particular needle was chosen due to stock availability, personal preference, or due to lesion characteristics. However, given that the baseline characteristics were similar between the two needle groups, it is less likely that the above mentioned factors would have impacted the study significantly. Further, the blinding of cytopathologist to the needle used and the original report is likely to mitigate the bias and improve the reproducibility of this study.

In conclusion, tissue adequacy of 22G FG FNB needle was superior to 22G RB FNB. Further, the type of needle seems to be the only modifiable factors that impacts adequate tissue acquisition. Multicentre prospective trials are needed to further evaluate the utility of different needle types.

**Table 3 Factors associated with number of cell groups-univariable and multivariable logistic regression analysis**

Factors	Univariable analysis			Multivariable analysis	
	< 50 cell clusters ( <i>n</i> = 138)	≥ 50 cell clusters ( <i>n</i> = 88)	<i>P</i> value	OR (95%CI)	<i>P</i> value
	<i>n</i> (%) or (mean ± SD)	<i>n</i> (%) or (mean ± SD)			
FNB needle used <sup>a</sup>					
22G RB needle	85 (62)	43 (49)	0.07	1.79 (1.02 - 3.12)	0.04
22G FG needle	53 (38)	45 (51)			
Gender					
Female	65 (47)	32 (36)	0.13		
Male	73 (53)	56 (64)			
Age (yr)	66.8 (12.3)	67.5 (11.7)	0.67		
Presence of trainee					
Yes	44 (32)	35 (40)	0.25		
No	94 (68)	53 (60)			
Location of lesion					
Gut wall lesions <sup>1</sup>	20 (14)	10 (11)	0.39		
Pancreatic lesions	78 (57)	45 (51)			
Lymph node	23 (17)	15 (17)			
Extramural lesions <sup>2</sup>	17 (12)	18 (21)			
Lesion size (mm) <sup>a</sup>	33.1 (16.9)	39.0 (21.2)	0.02	1.02 (1.00 - 1.03)	0.02
Lesion nature <sup>a</sup>					
Solid	129 (93)	87 (99)	0.09	0.13 (0.02 - 1.10)	0.06
Mixed	9 (7)	1 (1)			
Number of passes made	3.1 (0.8)	3.2 (0.8)	0.65		
Sonovue contrast					
Yes	3 (2)	2 (2)	1.00		
No	135 (98)	86 (98)			

<sup>a</sup>Parameters with a *P* < 0.10 on univariable analysis were included in the multivariable analysis and these parameters are indicated by an asterisk.

<sup>1</sup>Gut wall lesions include oesophageal, gastric, duodenal or rectal wall lesions.

<sup>2</sup>Extramural lesions do not include pancreatic lesions and lymph node. FNB: Fine needle biopsy; RB: Reverse bevel; FG: Franseen geometry.

## ARTICLE HIGHLIGHTS

### Research background

Many factors can affect endoscopic ultrasound fine needle biopsy (EUS-FNB) procedures tissue acquisition efficacy, with needle type and design being one of the possible factors.

### Research motivation

Currently, there is no direct comparison of tissue acquisition efficacy between reverse bevel (RB) and Franseen geometry (FG) needles.

### Research objectives

To look any for different in tissue acquisition performance between RB and FG needles, which can potentially be a modifiable factor to improve EUS-FNB accuracy in making a confident diagnosis.

### Research methods

A retrospective study of all EUS-FNA/FNB procedures by either 22G RB needle or 22G FG needle between January 2016 and February 2019. All cytology slides were reviewed by an independent gastrointestinal cytopathologist blinded to the needle used and the initial cytology report. The primary and secondary outcomes were to assess the sample adequacy using Euro-cytology criteria and the number of cell clusters, respectively.

### Research results

A total of 226 procedures were included. RB needle was used in 128 procedures and FG needle in 98 procedures. The baseline characteristics of both groups were comparable. On multivariable analysis, FG needle ( $P = 0.02$ ) and location of the lesion ( $P < 0.01$ ) were independently associated with adequate. Further, the use of FG needle ( $P = 0.04$ ) and the size of the lesion ( $P = 0.02$ ) were independently associated with acquisition of increased number of cell clusters.

### Research conclusions

FG needle is superior to RB needle in acquiring adequate tissue and attaining higher number of cell clusters for solid and mixed lesions.

### Research perspectives

Multicentre prospective trials are needed to further evaluate the utility of different needle types.

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## Retrospective Study

Kyoto classification in patients who developed multiple gastric carcinomas after *Helicobacter pylori* eradication

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**Institutional review board**

**statement:** This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 6, 2019 (approval no. S1909-U06).

**Informed consent statement:**

Patients were not required to give informed consent the study because the analysis used

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## Abstract

**BACKGROUND**

Endoscopic Kyoto classification predicts gastric cancer risk; however, the score in the patients with primary gastric cancer after *Helicobacter pylori* (*H. pylori*) eradication therapy is unknown.

**AIM**

To elucidate the Kyoto classification score in patients with both single gastric cancer and multiple gastric cancers developed after *H. pylori* eradication.

**METHODS**

The endoscopist recorded the Kyoto classification at the endoscope and the Kyoto classification score at the time of the first diagnosis of gastric cancer after *H. pylori* eradication. The score was compared between single gastric cancer group and multiple gastric cancers group.

anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** The authors declare that there is no conflict of interest.

**Data sharing statement:** No additional data are available.

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## RESULTS

The Kyoto score at the time of diagnosis of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. The multiple group had a significantly higher score than the single group ( $P = 0.016$ ). In the multiple gastric cancers group, all the patients (7/7) had 5 or higher Kyoto score, while in single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38).

## CONCLUSION

Patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers developed after *H. pylori* eradication, the endoscopic Kyoto classification score tended to be 5 or higher in patients with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

**Key Words:** Kyoto classification; Gastric cancer; *Helicobacter pylori*; Eradication therapy; Metachronous; Intestinal metaplasia

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**Core Tip:** This is a retrospective study to elucidate the endoscopic Kyoto classification score in patients with both single gastric cancer and multiple gastric cancers developed after *Helicobacter pylori* (*H. pylori*) eradication. The Kyoto score of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. In cases of multiple gastric cancers, the Kyoto classification score tended to be 5 or higher with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

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## INTRODUCTION

Eradication therapy for *Helicobacter pylori* (*H. pylori*), which is the most important risk factor for gastric cancer, is widely conducted<sup>[1-8]</sup>. Especially in Japan, *H. pylori* eradication therapy was approved by the national health insurance and the number of patients who received this therapy is rapidly increasing<sup>[9]</sup>. Gastric cancer may be found even after the eradication treatment, and risk factors for gastric cancer after eradication have been vigorously examined<sup>[6,10]</sup>. In particular, many researchers have focused on the relationship between endoscopic findings of the stomach and gastric cancer after eradication.

Recently, Kyoto classification has been devised as a method for evaluation of endoscopic findings of the stomach, and its validity is being studied<sup>[11-14]</sup>. The Kyoto classification score is the sum of scores for five endoscopic findings (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness) and ranges from 0 to 8. Atrophy, intestinal metaplasia, enlarged folds, and nodularity contribute to gastric cancer risk. Diffuse redness and regular arrangement of collecting venules (RACs) are related to *H. pylori* infection status<sup>[13,15]</sup>. Toyoshima *et al*<sup>[13]</sup> described that a Kyoto classification score  $\geq 2$  indicates *H. pylori* infection, and a Kyoto classification score  $\geq 4$  might indicate gastric cancer risk.

On the other hand, gastric cancer treatment is becoming less invasive, and the rate of treatment by local excision has increased<sup>[16-19]</sup>. With local treatment of the stomach, recurrence of gastric cancer can occur<sup>[20,21]</sup>. Although there is a relatively large number of reports on metachronous gastric cancer occurrence after *H. pylori* eradication therapy following endoscopic treatment for gastric cancer (gastric cancer diagnosis,



endoscopic treatment, *H. pylori* eradication, metachronous gastric cancer), there are few reports of multiple primary gastric cancers found after *H. pylori* eradication therapy (*H. pylori* eradication, multiple primary gastric cancer). As described above, with the spread of eradication therapy for *H. pylori*, the number of patients with gastric cancer diagnosed for the first time after eradication therapy is on the rise; therefore, the analysis of these cases would become more important. If gastric cancers are discovered during follow-up after the detection of primary stomach cancers, it is essentially difficult to distinguish whether those cancers occurred simultaneously or appeared at different time points since the growth speed of each gastric cancer would be different<sup>[22]</sup>. In the present study, synchronous gastric cancers and metachronous gastric cancers were collectively treated as multiple gastric cancers. As far as we know, few data exist on the association between Kyoto classification and primary gastric cancer occurrence post *H. pylori* eradication therapy. The purpose of this study was to develop Kyoto classification for differentiating between single and multiple gastric cancers in patients diagnosed with gastric cancer after *H. pylori* eradication.

## MATERIALS AND METHODS

### Study outline and patients

This retrospective study included 67 patients who were diagnosed with primary gastric cancer at least six months after the successful *H. pylori* eradication therapy between February 2010 to February 2019 in Toyoshima Endoscopy Clinic. We used data available from clinical charts and endoscopic database. We defined primary gastric cancer as pathologically diagnosed gastric cancer without past gastric neoplasm history. We divided these 67 gastric cancer patients into single gastric cancer patients and multiple gastric cancer patients. We defined multiple gastric cancer patients as those who had synchronous and/or metachronous gastric cancer. Patients without one or more follow-up endoscopy at our institution after primary gastric cancer diagnosis were excluded from the single gastric cancer patient group. This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 6, 2019 (approval No. S1909-U06). Written informed consent was obtained from all patients. All clinical investigations were conducted according to the ethical guidelines of the Declaration of Helsinki.

### *H. pylori* eradication therapy

Patients in whom *H. pylori* infection was confirmed underwent eradication therapy as described in our previous reports<sup>[5,23]</sup>. Patients who failed eradication therapy, received an additional treatment: First-line therapy included proton pump inhibitor (PPI), amoxicillin, and clarithromycin. Second-line therapy consisted of PPI, amoxicillin, and metronidazole. At least four weeks after the eradication therapy was completed, cure status was confirmed by <sup>13</sup>C urea breath test.

### Endoscopic procedure and Kyoto classification

Esophagogastroduodenoscopy was performed by certificated endoscopists. The patients underwent esophagogastroduodenoscopy either for screening, for a previous history of esophagogastroduodenal disease, present symptoms or abnormal findings on barium meal examination. Biopsy specimens were taken from lesions suspected to be gastric cancer, and the final diagnosis of gastric cancer was based on pathology results<sup>[3]</sup>. The endoscopists who performed each endoscopic procedure recorded the Kyoto classification of the endoscopic findings and the Kyoto classification score at the time of the first diagnosis of gastric cancer after *H. pylori* eradication was used for the analysis. A board certificated endoscopist reviewed each item of the Kyoto classification score. If there was a discrepancy in opinion, the final score was decided by joint discussion. The Kyoto classification of gastritis was based on the sum of the following five endoscopic scores using the range from 0 to 8. Gastric atrophy was classified according to the degree of mucosal atrophy as described by Kimura and Takemoto<sup>[20]</sup> with the Kimura-Takemoto classification of C-II and C-III scored as 1 while that of O-I to O-III scored as 2. Intestinal metaplasia was observed as grayish-whitish and slightly opalescent patches; intestinal metaplasia in the antrum was scored as 1 and intestinal metaplasia that was spread to the corpus was scored as 2. The presence of a fold that expanded to more than 5 mm was scored as 1. Nodularity was characterized by the appearance of multiple white raised lesions in the pyloric gland mucosa, and the presence of nodularity was scored as 1<sup>[24,25]</sup>. Diffuse redness referred to uniform redness involving the entire fundic gland mucosa, and the presence of diffuse

redness with RACs was rated as 1 and without RACs as 2<sup>[10,15]</sup>. After the diagnosis of gastric cancer, the tumor size, histological type, the Union for International Cancer Control cancer stage, and treatment modality were recorded in clinical chart and database.

### Statistical analyses

All statistical analyses were performed using JMP10 software (SAS Institute, Cary, NC, USA). Welch's *t* test was used to compare the means of continuous variables. Comparisons of nominal variables were performed using the  $\chi^2$  test or Fisher's exact test, as appropriate. A two-sided *P* value of < 0.05 was considered to indicate statistical significance.

## RESULTS

Of those diagnosed with gastric cancers at the Toyoshima Endoscope Clinic, 67 patients underwent eradication of *H. pylori* at least six months before the diagnosis, had no history of gastric cancer before eradication, and had no history of gastrectomy (the average observation period after eradication was 2.4 years). Seven cases of multiple gastric cancer were found (Table 1). In the multiple gastric cancers group, almost all the patients (6/7) had 5 points Kyoto score and one patient had 6 points Kyoto score. Three of these were metachronous gastric carcinomas and all of these patients had synchronous gastric carcinomas. In the three metachronous cases, the observation period from the primary gastric cancer diagnosis after *H. pylori* eradication therapy to the discovery of metachronous gastric cancer averaged 3.7 years.

We diagnosed 60 patients with primary gastric cancer after *H. pylori* eradication therapy. Of these, 22 patients without multiple gastric carcinomas (with the primary gastric cancer detected on average at 2.7 years after eradication) did not undergo follow-up endoscopy in the Toyoshima Endoscopy Clinic and were excluded. The remaining 38 patients received at least one follow-up endoscopy after the primary gastric cancer diagnosis so as to confirm the lack of multiple gastric cancer occurrence (mean observation period between primary gastric cancer diagnosis and the last follow-up endoscopy was 4.3 years); these were defined as single gastric cancer patients. Thus, patients with gastric cancer after *H. pylori* eradication were divided into single gastric cancer patients group (Single, 38 patients) and multiple gastric cancer patients group (Multiple, 7 patients) in the final analysis.

The baseline characteristics of the 45 gastric cancer patients that included 17 males and 28 females, with mean age of 67.0 years (range 43-86) are provided in Table 2. For these 45 cases, it took an average of 5.0 years from *H. pylori* eradication to the discovery of cancer. There was no difference in male to female ratio between single and Multiple groups, with the average age being higher in the Multiple group (65.6 years and 74.7 years, respectively, *P* = 0.039). The Kyoto score at the time of detection in 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the Single group, and 5.1 points in the Multiple group. The Multiple group had a higher score with a statistically significant difference (*P* = 0.016). In the Multiple gastric cancer group, all of the patients had 5 or higher Kyoto score, while in a Single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38). Enlarged folds, nodularity, and diffuse redness without RACs, the findings to suggest active *H. pylori* infection, were rarely observed [6.66% (3/45), 0, and 2.22% (1/45), respectively] in the background gastric mucosa in the 45 patients diagnosed with gastric cancer after successful *H. pylori* eradication therapy. All of the patients in multiple gastric cancer group had an open type atrophy and intestinal metaplasia of the corpus as background gastric mucosa. In the Single gastric cancer group, 68.2% (26/38) of the patients had an open type atrophy. Regarding intestinal metaplasia in the Single gastric cancer group, 31.5% (12/38) of the patients had no intestinal metaplasia, 21.0% (8/38) had intestinal metaplasia within antrum, and 47.3% (18/38) had corpus intestinal metaplasia. Map like redness was observed in 56.4% (22/38) and 71.4% (5/7) of the patients in Single and Multiple gastric cancer groups, respectively. Of the 45 cases of gastric cancer diagnosis after the eradication, most were graded as stage I (95.5% excluding 2 cases), pathologically grouped as intestinal type gastric cancer (93.3% excluding 3 diffuse type gastric cancer), and underwent curative endoscopic treatment (95.5% excluding 2 surgical cases). There was no difference in cancer size, stage, pathology, and treatment modality between the Single and Multiple groups.

Table 1 Characteristics of 7 cases of multiple gastric cancers after *Helicobacter pylori* eradication

Case	Sex	Age (yr), number of diagnosed lesions	Age (yr), number of diagnosed lesions
1	Female	79, 2	84, 1
2	Male	84, 2	87, 1
3	Female	71, 2	
4	Male	74, 1	77, 2
5	Male	71, 2	
6	Male	81, 3	
7	Male	63, 2	

## DISCUSSION

In this examination, we aimed to elucidate the endoscopic Kyoto score in patients with single and multiple gastric cancer after *H. pylori* eradication. We showed that patients who were diagnosed with gastric cancer after *H. pylori* eradication, had high Kyoto classification score of 4.0 on average, and in particular, multiple gastric cancer patients had an even higher score of 5.1. This result is in line with those shown in previous papers that argued about the importance of endoscopic follow-up even after the eradication of *H. pylori*, especially in advanced cases of gastritis<sup>[5,26,27]</sup>.

In our analysis, most of the post *H. pylori* eradication gastric cancers were the intestinal type, was consistent with the findings in past reports<sup>[3,28,29]</sup>. Intestinal type gastric cancers are often surrounded by intestinal metaplasia as background gastric mucosa<sup>[30]</sup>, and intestinal metaplasia is reportedly well known risk factor for metachronous gastric cancer<sup>[6,10,31]</sup>. Endoscopic gastritis grading, Kimura-Takemoto classification is also a very well-established classification that well describes the risk of gastric cancer, including gastric cancer after eradication<sup>[27,32,33]</sup>. In the Kyoto classification, positive findings on the items such as enlarged folds, nodularity, and diffuse redness are tended to disappear *via* *H. pylori* eradication therapy. On the other hand, both advanced intestinal metaplasia and atrophic gastritis, which have been established as risk factors for gastric cancer, did not improve in a short period of time<sup>[34]</sup>. We believe that multiple gastric carcinomas could occur in the situation of so called “point of no return”, in which gastric carcinogenesis cascade had progressed to the advanced stage due to the *H. pylori* infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes<sup>[35,36]</sup>.

This study has limitations. First, the study was conducted at a single institute and included a small number of patients. Future large scale and matched study is needed. Second, future longer observation could make some single gastric cancer cases into multiple cancer cases. Third, though we used Kyoto score at the time of primary cancer diagnosis, the score could change in the time course after the *H. pylori* eradication. Fourth, several possible confounding factors including dietary habits, family genetic history, and *H. pylori* virulent factors are not included in this examination.

In conclusion, patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers after eradication, the endoscopic Kyoto classification score tended to be at least 5 or higher with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

Table 2 Characteristics of the 45 gastric cancer after *Helicobacter pylori* eradication

Characteristics	Total (n = 45)	Single (n = 38)	Multiple (n = 7)	P value
Mean age (range), yr	67.0 (43-86)	65.6 (43-86)	74.7 (63-84)	0.039 <sup>a</sup>
Sex, n (%)				0.61
Female	17 (37.7)	15 (39.4)	2 (28.5)	
Male	28 (62.2)	23 (60.5)	5 (71.4)	
Kyoto score, average	4.02	3.81	5.14	0.016 <sup>a</sup>
Atrophic gastritis, score, n (%)	1.71	1.65	2.00	0.77
None, 0	1 (2.22)	1 (2.63)	0	
C-1, 0	0	0	0	
C-2, 1	7 (15.5)	7 (18.4)	0	
C-3, 1	4 (8.88)	4 (10.5)	0	
O-1, 2	7 (15.5)	6 (15.7)	1 (14.2)	
O-2, 2	7 (15.5)	6 (15.7)	1 (14.)	
O-3, 2	19 (42.2)	14 (36.8)	5 (71.4)	
Intestinal metaplasia, score, n (%)	1.28	1.15	2.00	0.048 <sup>a</sup>
None, 0	12 (26.6)	12 (31.5)	0	
Antrum, 1	8 (17.7)	8 (21.0)	0	
Corpus, 2	25 (55.5)	18 (47.3)	7 (100)	
Enlarged folds, score, n (%)	0.06	0.07	0	0.44
None, 0	42 (93.3)	35 (92.1)	7 (100)	
Present, 1	3 (6.66)	3 (7.89)	0	
Nodularity, score, n (%)	0	0	0	1.00
None, 0	45 (100)	38 (100)	7 (100)	
Present, 1	0	0	0	
Diffuse redness, score, n (%)	0.95	0.92	1.14	0.65
None, 0	3 (6.66)	3 (7.89)	0	
With RAC, 1	41 (91.1)	35 (92.1)	6 (85.7)	
Without RAC, 2	1 (2.22)	0	1 (14.2)	
Map like redness, yes	27 (58.6)	22 (56.4)	5 (71.4)	0.68
Mean size (range), mm	14.8 (1.0-120)	15.5 (1-120)	11.1 (1.0-35)	0.46
Pathology, n (%)				
Intestinal type	42 (93.3)	35 (92.1)	7 (100)	0.44
Diffuse type	3 (6.66)	3 (7.89)	0	
Stage, n (%)				0.98
I	43 (95.5)	36 (94.7)	7 (100)	
II	1 (2.22)	1 (2.63)	0	
III	1 (2.22)	1 (2.63)	0	
IV	0	0	0	
Treatment for gastric cancer, n (%)				
Endoscopy	43 (95.5)	36 (94.7)	7 (100)	0.54
Surgery	2 (4.44)	2 (5.26)	0	
Chemotherapy	0	0	0	

Best supportive care	0	0	0
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<sup>a</sup>Statistically significant. RAC: Regular arrangement of collecting venule.

## ARTICLE HIGHLIGHTS

### Research background

With the spread of eradication therapy for *Helicobacter pylori* (*H. pylori*), the number of patients with gastric cancer diagnosed for the first time after eradication therapy is on the rise; therefore, the analysis of these cases would become more important. Recently, Kyoto classification has been devised as a method for evaluation of endoscopic findings of the stomach, and its validity is being studied.

### Research motivation

As far as we know, few data exist on the association between Kyoto classification and primary gastric cancer occurrence post *H. pylori* eradication therapy.

### Research objectives

The purpose of this study was to develop Kyoto classification for differentiating between single and multiple gastric cancers in patients diagnosed with gastric cancer after *H. pylori* eradication.

### Research methods

This retrospective study included 67 patients who were diagnosed with primary gastric cancer at least six months after the successful *H. pylori* eradication therapy between February 2010 to February 2019 in Toyoshima Endoscopy Clinic. We used data available from clinical charts and endoscopic database. We defined primary gastric cancer as pathologically diagnosed gastric cancer without past gastric neoplasm history. We divided these 67 gastric cancer patients into single gastric cancer patients and multiple gastric cancer patients. We defined multiple gastric cancer patients as those who had synchronous and/or metachronous gastric cancer. Patients without one or more follow-up endoscopy at our institution after primary gastric cancer diagnosis were excluded from the single gastric cancer patient group.

### Research results

The Kyoto score at the time of diagnosis of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. The multiple group had a significantly higher score than the single group ( $P = 0.016$ ). In the multiple gastric cancers group, all the patients (7/7) had 5 or higher Kyoto score, while in single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38).

### Research conclusions

Patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers developed after *H. pylori* eradication, the endoscopic Kyoto classification score tended to be 5 or higher in patients with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

### Research perspectives

We believe that multiple gastric carcinomas could occur in the situation of so called "point of no return", in which gastric carcinogenesis cascade had progressed to the advanced stage due to the *H. pylori* infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes.

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## Observational Study

## Optimization of biliary drainage in inoperable distal malignant strictures

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**Institutional review board**

**statement:** The study was approved by the Institutional Review Board of the National Liver Institute, Menoufia University (IRB number IRB00003413) in April 2015. A consent form was signed by every patient.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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## Abstract

**BACKGROUND**

Given most patients with distal malignant biliary obstruction present in the non-resectable stage, palliative endoscopic biliary drainage with fully covered metal stent (FCMS) or uncovered metal stent (UCMS) is the only available measure to improve patients' quality of life. Half covered metal stent (HCMS) has been recently introduced commercially. The adverse effects and stent function between FCMS and UCMS have been extensively discussed.

**AIM**

To study the duration of stent patency of HCMS and compare it with FCMS and UCMS to optimize biliary drainage in inoperable patients with distal malignant obstruction. Secondary aims in our study included evaluation of patients' survival and the rates of adverse events for each type of stent.

**METHODS**

We studied 210 patients and randomized them into three equal groups; HCMS, FCMS and UCMS were inserted endoscopically.

**RESULTS**

Stent occlusion occurred in (18.6%, 17.1% and 15.7% in HCMS, FCMS and UCMS groups, respectively,  $P = 0.9$ ). Stent migration occurred only in patients with FCMS (8.6% of patients). Cholangitis and cholecystitis occurred in 11.4% and 5.7% of patients, respectively, in FCMS. Tumor growth occurred only in 10 cases among patients with UCMS after a median of 140 d, sludge occurred in nine, seven and one patients in HCMS, FCMS and UCMS, respectively ( $P = 0.04$ ).

**CONCLUSION**

revised according to the STROBE Statement-checklist of items.

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Given the prolonged stent functioning time, the use of HCMS is preferred over the use of UCMS and FCMS for optimizing biliary drainage in patients with distal malignant biliary obstruction.

**Key Words:** Obstructive jaundice; Endoscopic retrograde cholangio-pancreatography; Half covered metal stent; Fully covered and uncovered metal stents

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**Core Tip:** Given most patients with distal malignant biliary obstruction present in the non-resectable stage, palliative endoscopic biliary drainage with fully covered or uncovered metal stent is the only available measure to improve patients' quality of life. Half covered metal stent has been recently introduced commercially. The adverse effects and stent function between fully covered metal stent and uncovered metal stent have been extensively discussed. Given the prolonged stent functioning time, the use of half covered metal stent is preferred to the use of uncovered metal stent and fully covered metal stent for optimizing biliary drainage in patients with distal inoperable malignant biliary obstruction.

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## INTRODUCTION

Most patients with malignant obstructive jaundice present at the unresectable stage, when the management is restricted only to palliative measures. The common causes of distal malignant biliary strictures are cancer of the head of the pancreas and extra hepatic cholangiocarcinoma. Biliary drainage and decompression by metal stents to improve quality of life<sup>[1]</sup> is the therapeutic modality of choice by endoscopic or percutaneous routes, the percutaneous route is generally considered after many failed endoscopic trials<sup>[2]</sup> with or without chemo- or radiotherapy. At this stage, the prognosis is dismal, with 5-year survival rates of < 2%<sup>[3,4]</sup>. Endoscopic stenting by metal and plastic stents has been used to decompress biliary obstruction with varying success rates. The superiority of metal stents over plastic stents has been demonstrated in many meta-analyses' reports<sup>[5-7]</sup>. Metal stents offer better patency and wider caliber than plastic stents and thus there is less need for subsequent endoscopic retrograde cholangio-pancreatography (ERCP) procedure and re-stenting. Moreover, metal stents compared to plastic stents are more cost effective, especially in patients with longer survival, and decrease the number of ERCP procedures in centers with heavy ERCP volume.

Many types of metal stents are commercially available, including covered and uncovered stents. However, it is still questionable which type of stent is more suitable for drainage. The uncovered stents have higher rates of tumor ingrowth with subsequent occlusion and cholangitis (16%-46%)<sup>[8-14]</sup>, while fully covered stents obviate this disadvantage. In this type, however, the deposition of sludge and bacterial biofilm and tumor overgrowth may lead to occlusion and cholangitis. Stent migration as well as cholecystitis and pancreatitis are more likely to occur with the fully covered type<sup>[14]</sup>.

Although several meta-analyses have compared both types of stents, no definitive results have been obtained showing the merits of one type over the other type<sup>[15-18]</sup>. Recently, another type of metal stent (named half covered metal stent) was introduced to offer the advantages of both types, in which the distal half is covered to obviate tumor ingrowth occurring in uncovered stents and the proximal half is uncovered as a protective character against migration and cholecystitis, which occur as adverse events with covered metal stents<sup>[19,20]</sup>.

## MATERIALS AND METHODS

### Patients

This study is a single center three armed prospective randomized study, which was conducted at the National Liver Institute, Egypt, a tertiary referral, government-based, well-equipped center for gastroenterology and liver disease in Egypt, between May 2015 and May 2019.

A committee of endoscopists, interventional radiologists and hepatobiliary surgeons examined 6989 patients and their medical records in obstructive jaundice clinics at the same center for evaluation of medical management plan (Figure 1): 6344 had obstructive jaundice, and 5985 patients underwent ERCP for relieving biliary obstruction. In total, 210 patients were included in the current study under the diagnosis of unresectable malignant extra hepatic biliary obstruction. Resectability was based on clinical findings, imaging and laboratory investigations.

Inclusion criteria were as follows: Patient's age  $\geq 18$  years; elevated serum bilirubin levels  $\geq 1$  gm/dL and non-resectability or inoperability based on associated comorbid conditions. All patients signed an Arabic form of written informed consent before ERCP.

We excluded patients with undiagnosed or benign strictures; anatomical changes with previous gastric bypass or patients with duodenal or pyloric strictures not allowing the scope to pass to papilla even after dilatation. We excluded patients with cardiopulmonary co-morbidity, not suitable for general sedation for endoscopy. Patients with previous metal stents after occlusion were also excluded.

### Indications of ERCP

ERCP and stenting were considered if there was elevated serum bilirubin and dilatation of a proximal portion of the common bile duct and/or dilated common hepatic duct.

### Procedure-related complications

Early or procedure-related complications were defined as adverse events that occurred within 1 mo post-procedure. Serious procedure-related complications were reported when interventions or hospitalization were required<sup>[21,22]</sup>.

Clinical post-ERCP pancreatitis was considered if the patients developed elevated serum amylase  $> 3$  fold the upper normal limits on the first-day post-ERCP in presence of associated abdominal pain. The severity of pancreatitis was classified as mild, moderate and severe if the patient was hospitalized  $\leq 3$  d, 4-10 d and  $> 10$  d, respectively. Severe pancreatitis was also considered if the patient was admitted to the intensive care unit and/or if surgical intervention and radiological or endoscopic drainage were required regardless of hospitalization time.

Cholangitis was defined as persistence of jaundice and fever  $> 38$  °C for  $> 24$  h, leukocytosis  $> 15,000$ /dL. Cholecystitis was diagnosed when the patients developed positive Murphy's sign and distended gall bladder in sonographer examination<sup>[22]</sup>.

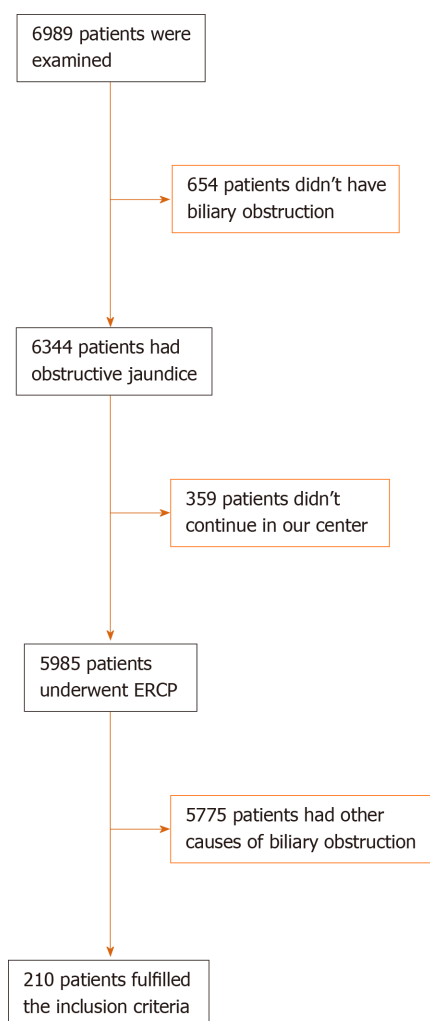
### Follow-up

All studied patients were followed up clinically at day 7, day 14 and day 30 and then after 6 mo post-ERCP. Successful procedure and stent deployment were considered when there was appropriate fluoroscopic positioning of the stent across the stricture in addition to normalization of serum bilirubin or at least a drop of total bilirubin by 30% from the baseline level by day 7 post-procedure.

Thereafter, patients were followed up monthly until death. Telephone follow-up was performed when patients could not return to the hospital, those with poor clinical condition and more than 6 mo after stent placement. In patients with recurrence of jaundice, reassessment of liver function with abdominal ultrasound was performed. When bile duct and intrahepatic biliary radicle dilation were observed during ultrasound or magnetic resonance cholangio-pancreatography examinations, subsequent ERCP was immediately performed.

### Randomization

Prior to ERCP procedure, studied patients were randomized for allocation to receive one of three stents: Half covered metal stent (HCMS), fully covered metal stent (FCMS) or uncovered metal stent (UCMS). Using 210 sealed, numbered, opaque envelopes by an endoscopist who did not perform the ERCP, one-third contained a card labeled "HCMS", one-third contained a card labeled "FCMS" and the final one-third contained a designed card labeled "UCMS". The procedure of randomization was



**Figure 1 Study flow chart.** ERCP: Endoscopic retrograde cholangio-pancreatography.

performed in the endoscopy unit by opening the sealed envelopes consecutively.

Subsequently, data were collected prospectively in previously designed form for data analysis and interpretation.

### **Ethical approval and consents**

This study was conducted according to the Declaration of Helsinki, and the protocol was approved by the ethics committee (for medical research) of Würzburg University and by the Institutional Review Board of the National Liver Institute, Menoufia University (IRB number IRB00003413) in April 2015. A consent form was signed by every patient.

### **Stent insertion**

All stents were inserted endoscopically. After successful cannulation, small papillotomy was performed, and the metal stent was deployed from its delivery system under careful endoscopic and fluoroscopic guidance. Dilatation by balloon or Sohendera dilators was done to determine accurately the desired length and facilitate stent insertion prior to procedure, provided that the distal end of the stent was passed from the papillary orifice. Prophylactic antibiotics were routinely given.

Types of stents: Three types of metal stents were used from Hanarostent (myocardial infarction-tech, Seoul, Korea): (1) HCMS, this stent is made from wires from braided nitinol, and the distal half of stent is coated with a silicone covering membrane, the proximal half is uncovered; (2) FCMS, this stent is similar in structure to HCMS, but it is coated with covering silicone membrane through its entire length; and (3) UCMS, this stent is made from wires from braided nitinol with no covering membrane through its entire length.



## Study endpoints

Endpoints of the study were stent patency, complications and patient survival.

## Stent dysfunction

According to Ung *et al*<sup>[23]</sup>, stent dysfunction is considered when the baseline level of serum bilirubin is doubled in addition to increase of serum alkaline phosphatase and/or occurrence of cholangitis. ERCP procedure was repeated in case of stent dysfunction if the general condition of the patient was fair. Stent patency was defined as the time from ERCP and stenting until stent dysfunction or death. Patients with functioning stents were censored until the end of the study or at date of their last follow-up or death.

## Analysis

We included 210 patients with inoperable distal malignant biliary obstruction based on the following assumptions: With the power of 80%,  $\alpha = 0.05$ , and the ratio of exposed to inoperable distal malignant biliary obstruction to those who with inoperable proximal malignant biliary obstruction = 1:2. The required sample size was determined using Epi info software.

Statistical analysis was performed using SPSS Statistics, version 26 (Armonk, NY, United States). A 2-sided *P* value of  $< 0.05$  was considered statistically significant. Simple random sampling and blind analysis were performed. Continuous variables were summarized as mean  $\pm$  standard deviation or median (range) for and number (%) for categorical variables. Categorical variables associations were tested using chi-square test. Continuous variables differences were tested among the three groups by parametric test (one-way analysis of variance test) when data were normally distributed or by non-parametric test (Kruskal Wallis test, post-hoc Tamhane test). The cumulative 6 mo and 12 mo survival probabilities were estimated using Kaplan-Meier survival curve, which was used to estimate median duration of each stent patency type. In each group, the log-rank test was used for comparison between the three stent types

# RESULTS

## Patient characteristics

Between May 2015 and May 2019, 210 patients met our inclusion criteria and were randomized for biliary drainage using HCMS (70 patients), UCMS (70 patients) or FCMS (70 patients).

Patient characteristics and demographic are shown in Table 1. In the studied patients, cancer head of the pancreas represented the most cause of biliary obstruction (67.1%, 68.6% and 65.7%) in HCMS, FCMS and UCMS, respectively. Distal cholangiocarcinoma represented 12.9%, 14.3% and 17.2% in HCMS, FCMS and UCMS, respectively. Gall bladder carcinoma represented 7.1%, 5.7% and 7.1% in HCMS, FCMS and UCMS, respectively, and ampullary carcinoma represented 12.9%, 11.4% and 10% in HCMS, FCMS and UCMS, respectively.

Patients in all groups were matched in regard to age, gender, baseline laboratory investigations and chemotherapy. Successful deployment was achieved in all patients. The operative time (time passed from selective cannulation until the end of procedure) was  $4.5 \pm 2.5$  min,  $4 \pm 1.5$  min and  $5 \pm 3.5$  min in HCMS, FCMS and UCMS, respectively. The X-ray time was  $2 \pm 1$  min,  $2 \pm 1.5$  min and  $2 \pm 1$  min, respectively.

Post-procedure outcomes are shown in Table 2. There was no procedure-related major adverse morbidity or mortality (Figure 1).

During follow-up, stent occlusion occurred in 36 out of 210 patients (18.6%, 17.1% and 15.7% in HCMS, FCMS and UCMS, respectively,  $P = 0.9$ ) (Table 2). Stent migration occurred only in patients with FCMS (8.6% of patients). Cholecystitis, probably due to mechanical obstruction of cystic duct orifice exerted by the stent, was observed in four patients with FCMS. None of the patients developed cholecystitis in the HCMS and UCMS groups. Cholangitis occurred in 5.7% of patients in the FCMS group.

## Early post-ERCP complications (within 1 mo)

Regarding procedure-related complications, pancreatitis occurred in 8.6%, 7.1% and 7.1% in HCMS, FCMS and UCM, respectively ( $P = 0.93$ ); all cases were mild. Minor bleeding occurred in 5.7%, 4.3% and 7.1% in HCMS, FCMS and UCM, respectively ( $P = 0.77$ ). Stent dysfunction occurred in six patients (stent migration occurred in one



Table 1 Patient characteristic among different groups

Number	Stent type, <i>n</i> = 70, <i>n</i> (%)			<i>P</i> value
	HCMS	FCMS	UMS	
Gender				0.86
Male	45 (64.3)	46 (65.7)	48 (68.6)	
Female	25 (33.7)	24 (34.3)	22 (31.4)	
Age, median (range)	67 (39-84)	65 (45-82)	64 (42-83)	0.37
Cholecystectomy	16 (22.9)	17 (24.3)	17 (24.3)	0.97
Cause of distal biliary obstruction				0.99
Cancer pancreas	47 (67.1)	48 (68.6)	46 (65.7)	
Distal cholangiocarcinoma	9 (12.9)	10 (14.3)	12 (17.2)	
Gallbladder cancer	5 (7.1)	4 (5.7)	5 (7.1)	
Ampullary cancer	9 (12.9)	8 (11.4)	7 (10.0)	
Laboratory investigations, mean $\pm$ SD				
Serum total bilirubin, mg/dL	15 $\pm$ 8.7	14.5 $\pm$ 5.6	16.1 $\pm$ 7.7	0.43
Serum direct bilirubin, mg/dL	13 $\pm$ 6.4	12.9 $\pm$ 4.1	13.2 $\pm$ 6.8	0.95
SGPT, UI/L	112 $\pm$ 90	110.7 $\pm$ 96.5	120.2 $\pm$ 90.3	0.80
SGOT, UI/L	146 $\pm$ 110.2	129.3 $\pm$ 106.2	142.4 $\pm$ 112.1	0.64
Albumin	4.1 $\pm$ 1.3	3.9 $\pm$ 1.4	3.8 $\pm$ 1.6	0.46
INR	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2	1.2 $\pm$ 0.2	0.94
Imaging				
Liver metastasis	2 (2.9)	1 (1.4)	1 (1.4)	0.78
PVT	1 (1.4)	1 (1.4)	2 (2.9)	0.78
Ascites	1 (1.4)	2 (2.9)	1 (1.4)	0.78
Clinical presentation				
Jaundice	57 (81.4)	55 (78.6)	55 (78.6)	0.89
Pain	34 (48.6)	31 (44.3)	34 (48.6)	0.84
Fever	9 (12.9)	8 (11.4)	9 (12.9)	0.96
Itching	16 (22.9)	15 (21.4)	18 (25.7)	0.83
Anorexia	27 (38.6)	26 (37.1)	20 (28.6)	0.41
Weight loss	44 (62.9)	42 (60.0)	45 (64.3)	0.87
Cholangitis	12 (17.1)	10 (14.3)	13 (18.6)	0.79
Operative time, time passed from selective cannulation till the end of procedure	4.5 $\pm$ 2.5 min	4 $\pm$ 3 min	5 $\pm$ 3.5 min	0.15
X-ray dose, time passed from selective cannulation till the end of procedure	2 $\pm$ 1 min	2 $\pm$ 1.5 min	2 $\pm$ 1 min	NA
Antibiotic				0.87
No	44 (62.9)	42 (60.0)	45 (64.3)	
Yes	26 (37.1)	28 (40.0)	25 (35.7)	
Previous chemotherapy				0.9
No	59 (84.3)	58 (82.9)	57 (81.4)	
Yes	11 (15.7)	12 (17.1)	13 (18.6)	
Radiotherapy				0.36

No	69 (98.6)	70 (100)	68 (97.1)	0.91
Yes	1 (1.4)	0 (0.0)	2 (2.9)	
Post-stenting chemotherapy				
No	55 (78.6)	56 (80.0)	57 (81.4)	
Yes	15 (21.4)	14 (20.0)	13 (19.6)	

HCMS: Half covered metal stent; FCMS: Fully covered metal stent; INR: International standard ratio; PVT: Production verification test; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; UMS: Uncovered metal stent.

**Table 2 Patient outcomes among different groups**

	Half and half stents, <i>n</i> (%)	Fully covered stents, <i>n</i> (%)	Un-covered stents, <i>n</i> (%)	<i>P</i> value
Successful deployment	70/70 (100)	70/70 (100)	70 /70 (100)	
Procedure related complications				
Major adverse events and or mortality	0	0	0	00
pancreatitis	6 (8.6 )	5 (7.1)	5 (7.1)	0.93
Minor bleeding	4 (5.7)	3 ( 4.3)	5 (7.1)	0.77
Post-ERCP complications				
Occlusion	13 (18.6)	12 (17.1)	11 (15.7)	0.9
Early stent adverse effect, within 1 mo	1 (1.4)	4 (5.7)	1 (1.4)	0.21
Sludge formation	9 (12.9)	7 (11.1)	1 (1.4)	0.04
Tumor Ingrowth	0 (0.0)	0 (0.0)	10 (14.3)	0.00003
Tumor Overgrowth	4 (5.7)	5 (7.1)	0 (0.0)	0.09
Cholangitis due to stent occlusion	7 (10.0)	8 (11.4)	7 (10.0)	0.95
Cholecystitis	0 (0.0)	4 (5.7)	0 (0.0)	0.02
Migration	0 (0.0)	6 (8.6)	0 (0.0)	0.002
Stent patency in d, median (95%CI)	614 (390.6-780.1)	256.0 (167.5-315.4) <sup>1,2</sup>	536 (323.1-743.9)	0.02
Follow-up in d, median (range)	112 (5-613)	109 (7-621)	108 (7-541)	0.82
Overall survival in d, median (95%CI)	129 (96.8-167.1)	114.0 (92.7 -165.4)	119.0 (89.9-160.1)	0.20

<sup>1</sup>Tamhane post-hoc *P* value < 0.05 between half and half stents and fully covered stents.

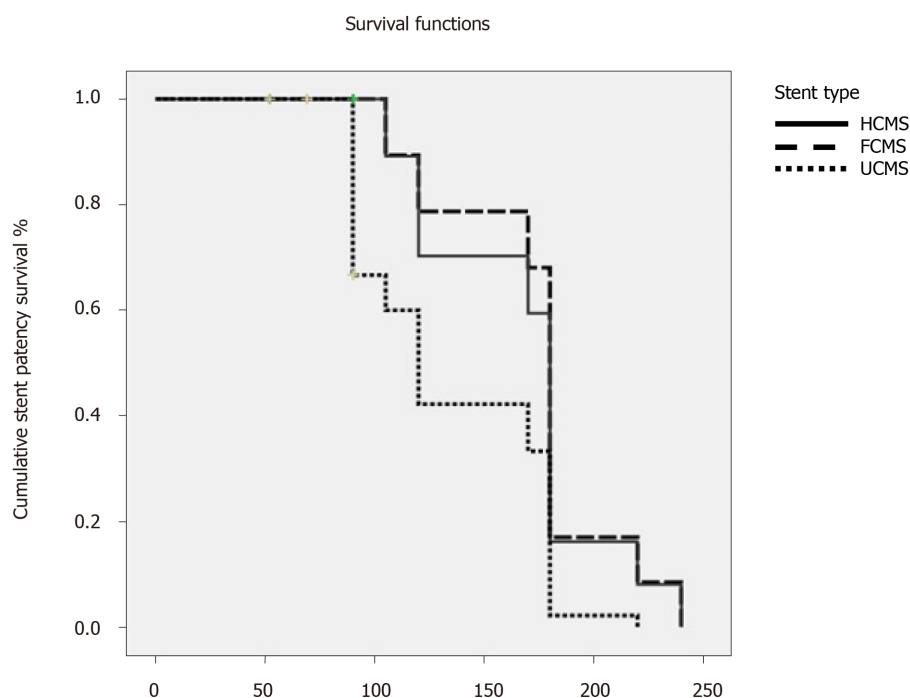
<sup>2</sup>Tamhane post-hoc *P* value < 0.05 between uncovered stents and fully covered stents. CI: Confidence interval; ERCP: Endoscopic retrograde cholangio-pancreatography.

patient in the FCMS group, cholangitis and stent obstruction occurred in one patient in each group, cholecystitis occurred in two patients in the FCMS group).

### **Late post-ERCP complications (after 1 mo)**

Tumor ingrowth was found in 10 cases among patients with UCMS (six cases associated with cholangitis) after a median of 140 d (range 52-541 d). Tumor overgrowth occurred in four FCMS patients, five patients with HCMS, and none in the UCMS developed tumor overgrowth. Sludge and stent occlusion occurred in nine, seven and one patient in HCMS, CMS and UCMS, respectively, *P* = 0.04).

Table 2 shows follow-up, survival and stent patency (Table 2). Patients' follow-up was 112, 109 and 108 d in HCMS, FCMS and UCMS, respectively. The median survival rates were 129 d 95% confidence interval (CI), 114 d 95%CI and 119 d 95%CI for HCMS, FCMS and UCMS, respectively, *P* = 0.000002). The median rate for stent patency was 614 d at 95%CI, 256 d at 95%CI and 526 d at 95%CI for HCMS, FCMS and UCMS, respectively, (*P* = 0.02) (Figure 2).



**Figure 2 Kaplan Meier survival curve of stent patency with different types of stents.** There is statistical significance regarding stent patency survival among the three types of stents, *P* value 0.000002 and log rank (Mantel-Cox) test 28.86, with median duration of stent patency of 170 d in HCMS stent type, 105 d in FCMS stent type and 90 d in UMS stent type. HCMS: Half covered metal stent; FCMS: Fully covered metal stent; UCMS: Uncovered metal stent.

## DISCUSSION

The newly designed HCMS was introduced commercially to get the merits of FCMS in terms of stent survival by preventing tumor ingrowth through the covering membrane. At the same time, the uncovered half of HCMS prevents the high rates stent migration and cholecystitis inherent in the FCMS.

We speculate that the technical characteristics of the anti-migration power offered by the proximal uncovered part of the HCMS might play significant roles in prevention of HCMS stent displacement either intra-ductal or distal to the duodenum. Moreover, the commercially available FCMS was characterized by inefficient radial or axial forces in addition to the inefficient covering portion, which may influence stent function or stent survival. To the best of our knowledge, this is the first randomized study comparing the three commercially available metal stents in palliation of non-resectable or inoperable malignant distal biliary strictures.

In our study, successful stent deployment was achieved in all patients, and there were no significant differences among the three types of stents in term of factors of clinical efficacy and serum bilirubin reduction. The early procedure related adverse events (pancreatitis and bleeding) were not significantly different among all groups. Early secondary re-interventions resulting from early stent dysfunction were reported in (one, four and one patients in HCMS, FCMS and UCMS respectively).

Early stent-related adverse events (within 1 mo) were reported in more patients with HCMS than those with FCMS and UCMS insertion. However, HCMS showed significantly better median patency rates than FCMS and UCMS. The main cause of HCMS and FCMS dysfunction was early occlusion with cholangitis due to sludge or overgrowth, while in UCMS, occlusion occurred due to tumor ingrowth. Stent migration was a more added cause for stent dysfunction. In our studied patients, there was no significant difference regarding procedure-related pancreatitis and bleeding among the studied groups.

Stent patency was higher among the HCMS group, given that the migration rate was less in comparison to the other two groups. Cholecystitis occurred more frequently in patients with a covered stent than the other two groups based on mechanical obstruction caused by covering membrane of the FCMS and/or the chemical injury caused by stent membrane.

Several clinical trials have discussed the advantage of each type of previously available stent (FCMS and UCMS). These studies have shown the superiority of FCMS over UCMS in term of stent patency and function in patients with malignant distal

biliary obstruction<sup>[6,7,14,23-29]</sup>. Another advantage of covered stents over UCMS is the ease of removability, given its lack of adherence to tumorous tissues.

Since 2011, five meta-analysis studies comparing FCMS and UCMS have been published. However, these studies have evaluated heterogeneous cohorts with retrospective and prospective nature. Moreover, percutaneous and endoscopic approaches of deployments were used<sup>[15,23,30-32]</sup>.

In an analysis by Saleem *et al*<sup>[30]</sup>, the patency of FCMS was significantly longer than that of UCMS. Although the stent obstruction was detected at similar a rate in both groups, patients with FCMS tended to develop stent dysfunction later than patents with UCMS<sup>[30,33]</sup>. Stent migration was noticed significantly more in another meta-analysis<sup>[31]</sup> among patients with FCMS; however, patients experienced no difference in stent patency within the first 6 mo post-procedure. In another three meta-analyses<sup>[15,31,32]</sup>, there was no reported difference in term of stent patency, patient survival or adverse events between both groups.

In our patients, we designed the current study to apply a closer look and to shed more light on the newly introduced stent. The HCMS has a covering membrane in its distal portion to avoid tumor ingrowth. At the same time, it has the advantage of UCMS in terms of an absence of covering membrane in its proximal part, which allows bile to flow through its mesh from the cystic duct and hence avoidance of cholecystitis associated with FCMS. At the same time, it devotes its proximal portion to anti-migration maintaining efficient axial and radial forces that in turn prevent stent displacement.

In our patients with HCMS insertion, none developed stent migration and tumor ingrowth, similar to patients with UCMS insertion. At the same time, none of them developed stent migration or cholecystitis like patients with UCMS insertion.

The discrepancies between the findings of our study and the findings of aforementioned meta-analyses studies may be due to the use of the newly introduced stent, the heterogeneity in the study designs, degree and level of stricture, the characteristics of tumors that cause biliary stricture and stent configurations and materials.

Aiming to reduce the confounding bias of our findings in correspondence to stent materials, we used three types of stents from the same manufacture. So, our findings may not be generalizable to other types of metal stents. Given the results of our study, we supposed that HCMS stents are the best choice in this group of patients due to the inherent advantages of both types of its characteristics. However, early occlusions of the HCMS and FCMS were noticed due to tumor overgrowth, and these finding were surprising and controversial, when compared with other studies<sup>[15,20,23,30-34]</sup>. Conio *et al*<sup>[20]</sup> have explained that this overgrowth may be due to a created tissue hyperplasia induced by inflammatory reaction caused by the membrane covering of the stents rather than a true tumor overgrowth. And so, the overgrowth material is principally due to granulation tissue rather than tumorous tissue<sup>[20]</sup>.

In our study and Lee *et al*<sup>[29]</sup>, the FCMS patency was not significantly better than UCMS. Notably, stent migration occurred more in patients with FCMS. However, with use of HCMS, the migration was similar to UCMS and less than FCMS. Similar findings regarding the absence of stent migration in patients treated with UCMS were found in previously published studies<sup>[5,23-30,33]</sup>. In our patients and in Conio *et al*<sup>[20]</sup>, the migration rate for FCMS was significantly higher than in other studies<sup>[27,28]</sup>. Probably in these trials, the endoscopists used stents with an anti-migration system consisting of a portion of uncovered flares at both ends<sup>[24]</sup>. However, Yang *et al*<sup>[15]</sup> found no clinical usefulness of the anti-migration design<sup>[15,34]</sup>.

Mechanical closure of the orifice of cystic and pancreatic ducts by the covering membrane of FCMS resulted in higher rates of post-ERCP cholecystitis and pancreatitis<sup>[14,19,20,24,26]</sup>. To avoid post-ERCP pancreatitis with FCMS, Conio *et al*<sup>[20]</sup> advised not to place long FCMS. The post-ERCP cholecystitis could be avoided with use of HCMS or UCMS<sup>[20]</sup>. However, Isayama *et al*<sup>[14]</sup> found that the post-ERCP cholecystitis occurred only in cases with cystic duct invasion rather than with the use of FCMS. In our study, no significant difference was found among the different groups regarding pancreatitis, although Isayama *et al*<sup>[14]</sup> found significantly more cases of mild pancreatitis in FCMS *vs* UCMS (8.7% *vs* 1.8%)<sup>[14]</sup>. The difference in procedure-related pancreatitis may be due to the routine performance of small papillotomy in our patients to facilitate stent deployment. However, post-ERCP pancreatitis is a multifactorial adverse event.

The present study has many strengths, including its prospective and randomization design, comparison among three types of metal stents, the stent material was from the same manufacture, the relatively large number of included patients and the close follow-up period to assess stent patency and patient's survival.

This study was limited by being a single center study with possible lack of generalizability to other centers. However, this factor is unlikely to compromise the results of our study, based on the relatively large number of included patients and the high volume of ERCP procedure conducted in our center.

The study was also limited by the heterogeneity of included patients regarding the cause of biliary obstruction, the use of pre- and post-procedure anti-cancer therapies in some patients and possible lack of possible generalizability to other types of metal stents from other manufacturers. In addition, quality of life and cost were not assessed.

In conclusion, given the prolonged stent function, in terms of longer patency and decreased rates of migration, cholecystitis and tissue ingrowth, the use of HCMS is preferred over the use of UCMS and FCMS in palliation for distal malignant biliary obstruction. Our results need to be supported by additional studies. Cost and patients' quality of life should be addressed.

## ARTICLE HIGHLIGHTS

### Research background

Most patients with malignant obstructive jaundice present at the unresectable stage, when the management is restricted only to palliative measures. The common causes of distal malignant biliary strictures are cancer of the head of the pancreas and extrahepatic cholangiocarcinoma. This is mostly treated with metal stent insertion placement for biliary drainage.

### Research motivation

Many types of metal stents are commercially available, including covered and uncovered stents. However, it is still questionable which type of stent is more suitable for drainage, and half covered metal stents have been recently introduced.

### Research objectives

To study the adverse effects and functionality of the recently introduced half covered metal stents *vs* fully covered and uncovered ones.

### Research methods

We studied 210 patients and randomized them into three equal groups to investigate the functionality and performance of the three different types of metal stents which are the newly introduced half covered *vs* fully and uncovered metal stents.

### Research results

The half covered metal stents showed no significant difference in the incidence of occlusion while significantly less incidence of migration than uncovered stents. In addition, the half covered stents showed significantly more functioning and patency time.

### Research conclusions

The use of half covered metal stent is preferred over the use of uncovered metal stent and fully covered metal stent for optimizing biliary drainage in patients with distal inoperable malignant biliary obstruction.

### Research perspectives

Our findings will appeal to endoscopists and promote the use of half covered metal stents for biliary drainage of malignant obstructive jaundice because of the decrease in adverse events and migration and the increase in functioning time.

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## Endoscopic approach to gastric remnant outlet obstruction after gastric bypass: A case report

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## Abstract

### BACKGROUND

Acute gastric remnant bleeding is a rare complication of bariatric surgery. Furthermore, acute bleeding from the gastric remnant resulting in gastric remnant outlet obstruction has not been described previously. Endoscopic management of gastric remnant bleed has been challenging due to difficulty accessing the excluded stomach. Traditionally, this necessitates surgical intervention. Recently, however, the adoption of endoscopic ultrasound-directed transgastric intervention provides an alternative approach to management.

### CASE SUMMARY

A 65-year-old male with a prior gastric bypass presented with the sudden onset of progressive abdominal distension, nausea, and melena of two days duration. His imaging illustrated a massively distended stomach. A nasogastric tube did not result in drainage of fluid or decompression of his abdomen. His endoscopy revealed a normal-appearing gastro-jejunal anastomosis and confirmed the distended "fluid"-filled gastric remnant. An endoscopic ultrasound-directed gastrogastrostomy was created to decompress the gastric remnant. Two liters of blood was suctioned before a large adherent clot was visualized in the gastric antrum. The patient underwent emergent angiography with embolization of the gastroduodenal artery. He was discharged with a stable hemoglobin level and resolution of symptoms. Healing superficial gastric ulcers were visualized on a follow-up endoscopy. Gastric biopsies were consistent with *Helicobacter pylori* infection for which the patient was treated, and successful eradication was achieved.

### CONCLUSION

This patient benefited from a timely diagnosis and effective therapy of an acute gastric remnant obstruction from a bleeding ulcer with endoscopic ultrasound-

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directed transgastric intervention.

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**Core Tip:** The gastric remnant can be safely and effectively accessed by endoscopic ultrasound-directed transgastric intervention by the formation of a gastrogastrostomy using a lumen apposing metal stent to treat several conditions, including but not limited to bleeding gastric ulcers and gastric outlet obstruction among patients who have previously undergone Roux-en-Y gastric bypass. This method is an effective, safe, and less invasive alternative to surgery.

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## INTRODUCTION

Complications following Roux-en-Y gastric bypass (RYGB) can be acute or chronic and can be potentially life-threatening if not immediately recognized and treated. Complications of the pancreatobiliary limb (PBL) and the excluded stomach after RYGB have been reported. However, acute gastric remnant bleeding is an infrequent complication of bariatric surgery. Endoscopic management with either push or balloon enteroscopy is challenging due to technical difficulties in accessing the excluded stomach. In most cases, surgical intervention is necessary and is the standard approach<sup>[1,2]</sup>.

We present a patient who had a timely diagnosis and successful treatment with endoscopic decompression using a lumen-apposing metal stent (LAMS). This approach is more recently described under the spectrum of endoscopic ultrasound (EUS) directed transgastric intervention (EDGI). EDGI defines any EUS-directed procedure requiring transgastric intervention to adjacent luminal structures, including the gastric remnant among RYGB patients<sup>[3]</sup>. Several studies have shown EDGI to be more effective than balloon enteroscopy, and equally as effective as a surgical intervention with fewer complications.

## CASE PRESENTATION

### Chief complaints

A 65-year-old male presented with the sudden onset of progressive abdominal distension.

### History of present illness

The patient's symptoms started two days prior and included associated nausea, dry-heaves, lightheadedness, and melena.

### History of past illness

His only medical history is a remote RYGB eight years prior for weight loss.

### Personal and family history

The patient denied further medical history. He also denied a history of tobacco, alcohol, and NSAID use. His father died of myocardial infarction at age 70 and his mother was diabetic. He denied a family history of gastrointestinal malignancy.

**Physical examination**

On presentation, he was afebrile and hemodynamically stable. However, he appeared pale with conjunctival pallor. The abdomen was distended but non-tender with normal bowel sounds. The rectal exam exhibited melena.

**Laboratory examinations**

Complete blood count and complete metabolic panel were notable for a hemoglobin of 12 g/dL and hematocrit of 35.8%, which were near his baseline. His blood urea nitrogen was 23 mg/dL and his creatinine was 0.8 mg/dL. The remainder of these laboratory examinations, including liver enzymes and coagulation studies, were within normal limits.

**Imaging examinations**

Chest X-ray was normal. A subsequent computerized tomography scan with intravenous contrast illustrated a massively distended stomach, which was "fluid"-filled (Figure 1).

**Further hospital course**

A nasogastric tube was inserted, which did not result in any immediate drainage of fluid or decompression of his abdomen.

He immediately underwent an emergent upper endoscopy and EUS for decompression of the gastric remnant. The endoscopy revealed a normal-appearing gastro-jejunal anastomosis without marginal ulceration or evidence of active or recent bleeding in either limb. EUS confirmed the distended "fluid"-filled gastric remnant. We then proceeded to decompress the gastric remnant by creating a gastro-gastrostomy using a Hot AXIOS™ LAMS delivery system. Fine needle aspiration with a 19-gauge needle into the "fluid"-filled gastric remnant revealed maroon aspirate. A safe window for stent placement was found using doppler guidance. A 15 mm × 10 mm AXIOS™ stent was deployed, first by rapidly puncturing the fluid cavity under doppler guidance with the AXIOS™ tip electrified at 90 Watts, then by the ultrasound-controlled deployment of the inner phalange of the stent, and then finally by the endoscopy-controlled deployment of the outer phalange in the lumen of the gastric pouch. Upon deployment, maroon-colored blood immediately started draining. After extensive suctioning, the gastric remnant was decompressed (Figure 2).

Next, balloon dilatation of the stent allowed a gastroscope to access the gastric remnant. Approximately two liters of blood was suctioned before a large adherent clot was visualized in the gastric antrum. Fresh blood was observed oozing around the clot (Figure 3). Endoscopic therapy was not pursued due to the sheer size of the clot and concern of stent dislodgement. The patient was sent for emergent angiography with embolization of the gastroduodenal artery (Figure 4). He remained hospitalized for two additional days. He was discharged with a stable hemoglobin level and resolution of abdominal distension and bleeding. After a three-week interval, a repeat endoscopy for evaluation of the gastric remnant through the gastrogastric fistula was performed. Healing superficial gastric ulcers were visualized (Figure 5). The LAMS was left in place with plans for removal at an interval date. Gastric biopsies were consistent with *Helicobacter pylori* infection for which the patient was treated, and successful eradication was achieved.

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**FINAL DIAGNOSIS**

*Helicobacter Pylori* infection-induced gastric remnant ulcer bleeding causing outlet obstruction.

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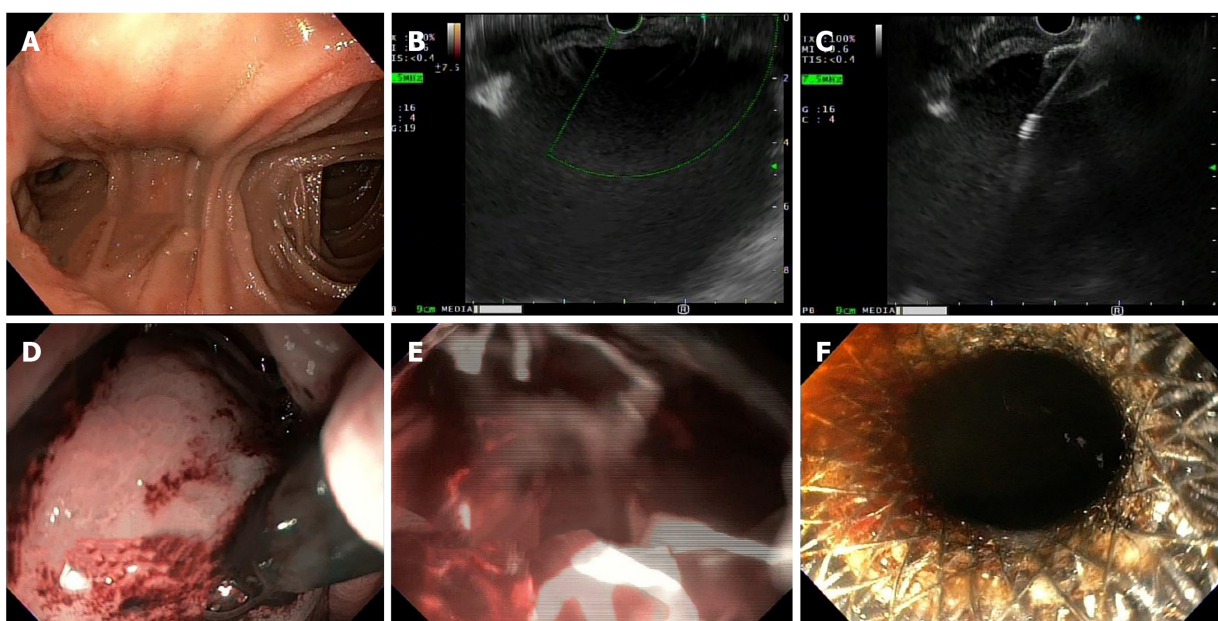
**TREATMENT**

Endoscopic ultrasound-directed transgastric intervention, gastroduodenal artery embolization, and triple therapy including Clarithromycin, Amoxicillin, and Pantoprazole dosed twice daily for a duration of 14 d. This was the treatment of choice given low rates of Clarithromycin resistance in our area and lack of patient risk factors for Clarithromycin resistance.





Figure 1 Computerized tomography scan revealing gastric remnant outlet obstruction.



**Figure 2 Endoscopy.** A: Healthy-appearing mucosa of Roux-en-Y; B: Gastric distension visualized on Endoscopic ultrasound; C: Introduction of Lumen-Apposing Metal Stent; D: Endoscopic view of Lumen-Apposing Metal Stent placement; E: Immediate decompression with flow of blood through stent; and F: Successful endoscopic ultrasound guided gastro-gastrostomy using Lumen-Apposing Metal Stent.

## OUTCOME AND FOLLOW-UP

The patient recovered well without complications or weight gain. He completed the course of triple therapy and has not had a recurrence of symptoms. Successful eradication was achieved. He is scheduled for retrieval of his lumen apposing metal stent.

## DISCUSSION

Marginal ulcers comprise the vast majority of gastrointestinal bleeding complications in patients who have undergone a RYGB, with an estimated incidence of 0.6%-16%<sup>[4]</sup>. Marginal ulcers are easily diagnosed and treated with conventional upper endoscopy. However, ulceration of the gastric remnant or duodenum is rare, with approximately 25 reported cases in the literature<sup>[5-10]</sup>. Risk factors for developing such ulcers include hyperacidity of the gastric remnant without the buffering effect of ingested food, bile acid reflux, NSAIDs use, and *Helicobacter pylori* infection<sup>[9]</sup>. Most instances of obstruction of the gastric remnant were due to malignancy. Pyloric stenosis was

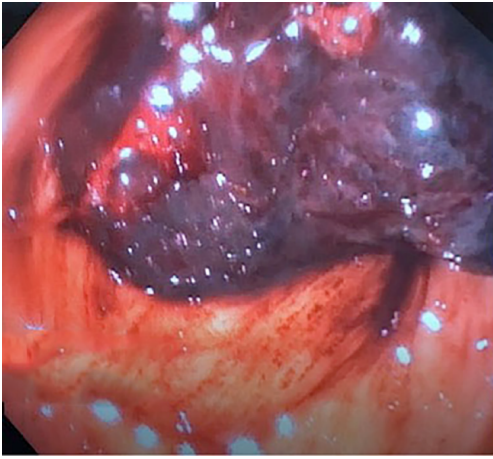


Figure 3 A large clot in gastric antrum of the excluded stomach.

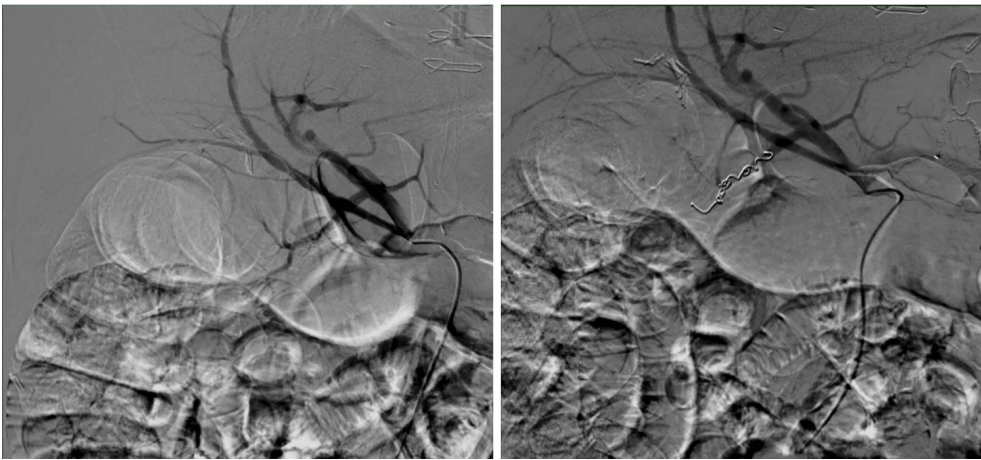


Figure 4 Angiography and embolization of gastrooduodenal artery.

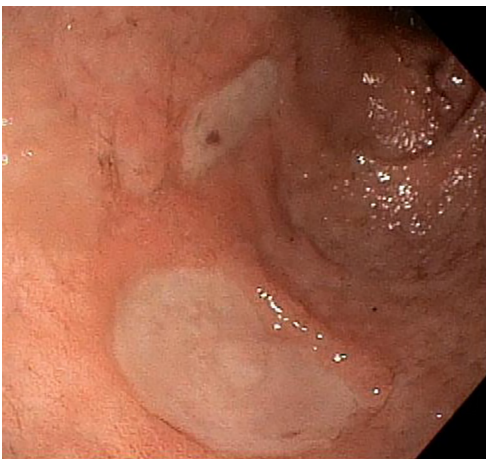


Figure 5 Healing gastric ulcers on follow up endoscopy.

reported as a benign etiology in only one case study<sup>[11]</sup>. We were unable to uncover any instances of outlet obstruction of the gastric remnant caused by bleeding ulcers.

Historically, ulceration of the gastric remnant and duodenum has been treated by laparotomy and endoscopy through either a surgical gastrostomy or by enteroscopy. Hakim *et al*<sup>[9]</sup> describe two cases of afferent limb bleeding with successful exploration and treatment by push enteroscopy or single-balloon enteroscopy<sup>[9]</sup>. However, this



method is not always successful due to difficulty intubating the excluded segment. The low success rate is due to difficulty reaching the duodenum and gastric remnant<sup>[1,2]</sup>.

Our case supports the use of an alternative and less invasive approach to gastric outlet obstruction of the gastric remnant through EUS-directed creation of gastrogastrostomy with a LAMS. This method is diagnostic, giving the operator the ability to visualize the pathological process by an antegrade approach. It is also therapeutic, forming a conduit by which built up secretions and blood can drain into the patent roux limb, as well as allowing for endoscopic hemostasis to be attempted. The necessity to treat pancreaticobiliary disease with ERCP following a RYGB has resulted in the advent of EUS-directed transgastric ERCP (EDGE). More recently, this method has been grouped under the umbrella term "EDGI", a phrase coined by Krafft *et al*<sup>[3]</sup> to highlight the increasing use of this method for accessing the PBL for other diagnostic and therapeutic interventions in addition to ERCP<sup>[3]</sup>.

Studies on EDGE have shown EUS-directed access of the gastric remnant to be clinically safe and effective. Xu *et al*<sup>[12]</sup> describe a case of bile leak that was successfully treated with ERCP performed through a gastrogastrostomy formed by EUS-directed LAMS placement<sup>[12]</sup>. The high success rate of accessing the PBL by EUS guidance is highlighted by Kedia *et al*<sup>[13]</sup>. In their study, technical success, which was defined as successful deployment of LAMS to form either gastrogastrostomy or jejunogastrostomy, was 100%. Clinical success, which was defined as successful endoscopy through the LAMS, was 90%. Complications included LAMS migration at the index procedure in three patients and jejunal perforation with the insertion of the duodenoscope through the LAMS in one patient. Importantly, none of these patients suffered from clinical sequelae or necessitated surgical intervention<sup>[13,14]</sup>.

An international, multicenter study of patients who demonstrated the safety and efficacy of EDGI for either benign or malignant gastric outlet obstruction. Not only was the success rate comparable to the surgical approach, but it also was successful as salvage therapy for patients who failed surgery. Adverse events occurred in 11.5%. In comparison, the complication rate of surgical gastrojejunostomy has been reported to be as high as 40%<sup>[15]</sup>. Follow-up data after EDGE for these patients revealed no symptom recurrence after a mean follow-up of 7.9 wk in the clinically successful cases<sup>[16]</sup>. Though none of these patients presented with bleeding ulcers causing outlet obstruction of the gastric remnant, as in our case, these studies provide evidence for the safety and efficacy of EUS-directed gastrogastrostomy formation with LAMS.

Krafft *et al*<sup>[3]</sup> provide direct evidence for clinical and technical effectiveness, as well as safety for EDGI in cases with indications other than ERCP. Their multicenter, retrospective analysis included patients with RYGB who underwent EDGI for indications including gastroduodenal mass, duodenal ulcer perforation, biopsy of pancreatic mass, drainage of pancreatic fluid collections, and common bile duct dilation. Technical success, defined as successful transmural fistula creation using LAMS, and clinical success, defined as the attainment of diagnosis and partial or complete symptom relief, each showed rates of 100% in this small study<sup>[3]</sup>.

## CONCLUSION

Based on our literature review, this is the first described case of an outlet obstruction of the gastric remnant caused by a bleeding ulcer. This case was successfully managed by the creation of a gastrogastrostomy using a lumen-apposing metal stent. Our case adds to the literature evidence for safe and efficacious access to the gastric remnant by EDGI. It sets a precedent for the use of this technique in treating similar clinical scenarios. This method is an effective, safe, and less invasive alternative to surgery.

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## Small invasive colon cancer with adenoma observed by endocytoscopy: A case report

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### Abstract

#### BACKGROUND

Endocytoscopy is a next-generation endoscopic system that facilitates real-time histopathologic endoscopic diagnosis of colorectal lesions by virtue of its 520 × maximum magnification.

#### CASE SUMMARY

We present the case of a 63-year-old man with sigmoid colon cancer who was regularly referred for follow-up colonoscopy after endoscopic resection of T1 rectal cancer. Colonoscopy revealed a 12 mm reddish polyp, including a depression and a flat area in the sigmoid colon. Endocytoscopic observation showed unclear gland formation and agglomeration of distorted nuclei (depression), suggesting a submucosal invasive (T1) cancer. In the flat area, slit-like smooth lumens and regular pattern of fusiform nuclei were found, suggesting an adenoma. On the basis of these endocytoscopic findings, we predicted this lesion as T1 cancer (depression) with adenoma (flat area) and performed endoscopic resection corresponding to the final histopathological diagnosis.

#### CONCLUSION

We could perform an optical diagnosis of T1 sigmoid cancer with adenoma by using endocytoscopy before treatment.

**Key Words:** Endocytoscopy; T1 colorectal cancer; Adenoma; Optical diagnosis; Case report

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**Core Tip:** Endocytoscopy is a next-generation endoscopic system. Endocytoscopic observation suggested that a 12 mm reddish polyp, including a depression and a flat area in the sigmoid colon was T1 cancer (depression) with adenoma (flat area). We could perform an optical diagnosis of the lesion by using endocytoscopy before treatment.

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## INTRODUCTION

Integrated-type endocytoscopy (CF-H290ECI; Olympus Corp, Tokyo, Japan) is a next-generation endoscopy commercially available in Europe, the Middle East, Hong Kong, and Japan. An endocytoscope comprises a contact light microscopy system (magnification,  $\times 520$ ; focusing depth, 35  $\mu\text{m}$ ) integrated into the distal tip of a colonoscope. It enables in vivo microvascular evaluation with the narrow band imaging mode and cellular visualization after staining with 0.05% crystal violet (1% methylene blue may be added if necessary)<sup>[1-3]</sup>. In the diagnosis of colorectal lesions, endocytoscopy is particularly useful not only for differentiating neoplastic and non-neoplastic lesions but also for diagnosing the depth of invasion of colorectal cancer<sup>[4,5]</sup>. In addition, endocytoscopy has recently been reported to be an effective modality for the differential diagnosis of low-grade colorectal adenomas<sup>[6]</sup>. In the present case, we accurately predicted the histopathological findings of a two-component lesion by using endocytoscopy before treatment.

## CASE PRESENTATION

### Chief complaints

A 63-year-old man was regularly referred for follow-up colonoscopy after endoscopic resection of T1 rectal cancer.

### Personal and family history

The patient consumed alcohol twice a week but denied smoking cigarettes. His family history was negative for any gastrointestinal cancer.

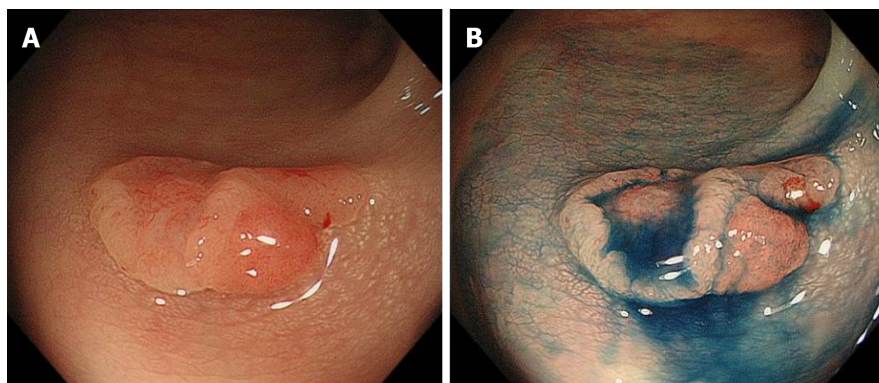
### History of past illness

The patient was treated for T1 rectal cancer *via* endoscopic resection 4 years previously. The result of the histological diagnosis was adenocarcinoma (well to moderately differentiated), with a depth of invasion of 9000  $\mu\text{m}$  (T1), negative lymphovascular invasion, budding grade 1, and negative horizontal and vertical margins. We considered the risk of lymph node metastasis (LNM), and recommended that he undergo additional surgery. However, he refused to undergo surgery and was consequently regularly referred for follow-up colonoscopy. In addition, he had high blood pressure and diabetes.

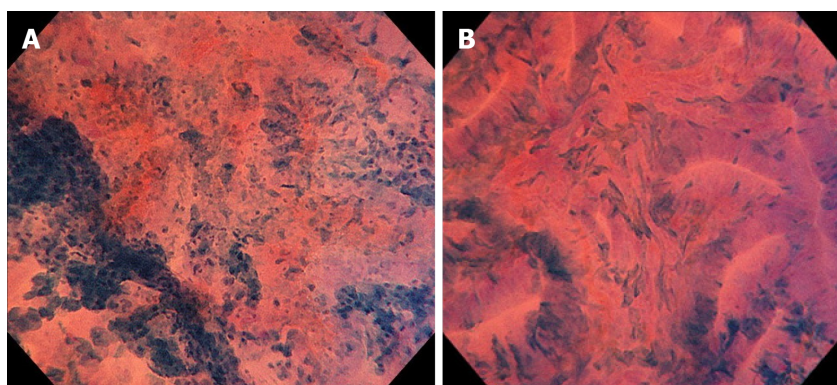
### Imaging examinations

Colonoscopy revealed a 12 mm reddish polyp in the sigmoid colon (Figure 1A). We could recognize a depression on the left side and a flat area on the right side with indigo carmine staining (Figure 1B). On the left side of the lesion (depression), unclear gland formation and agglomeration of distorted nuclei strongly stained by methylene blue were visible with endocytoscopy, suggesting a submucosal invasive cancer (Figure 2A). On the right side of the lesion (flat area), slit-like smooth lumens and a regular pattern of fusiform nuclei were found, suggesting an adenoma (Figure 2B).





**Figure 1 The colonoscopy.** A: Colonoscopy revealed a 12-mm reddish polyp in the sigmoid colon; B: Indigo carmine staining revealed a depression on the left and a flat area on the right side.



**Figure 2 Endocytoscopy of the lesion.** A: On the left side of the lesion (depression), unclear gland formation and agglomeration of distorted nuclei strongly stained by methylene blue were visible with endocytoscopy, suggesting a submucosal invasive cancer; B: On the right side of the lesion (flat area), slit-like smooth lumens and a regular pattern of fusiform nuclei were found, suggesting an adenoma.

## FINAL DIAGNOSIS

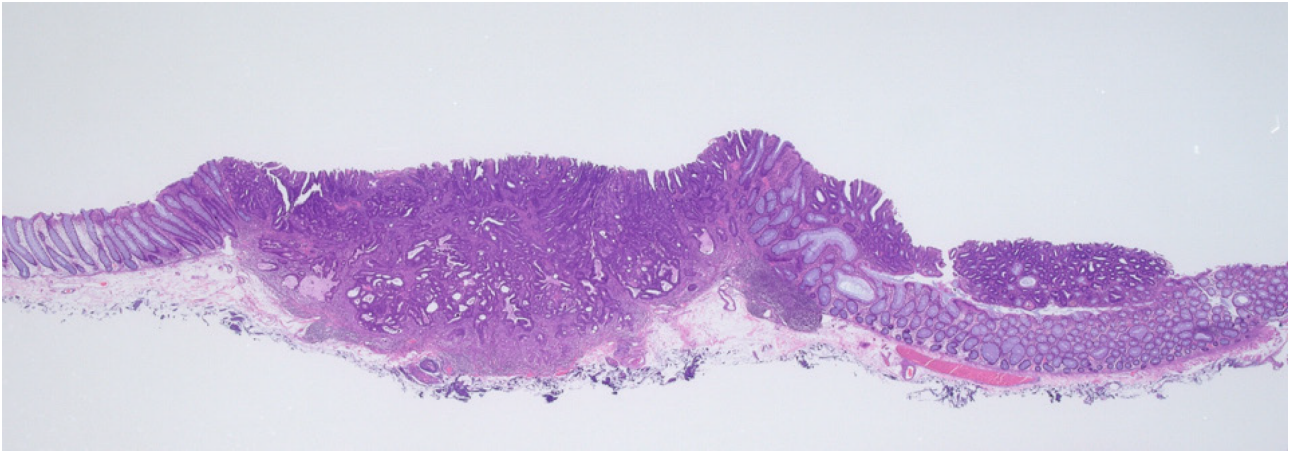
T1 sigmoid colon cancer with adenoma. The left side of the lesion corresponded to T1 cancer and the right side corresponded to adenoma (Figure 3).

## TREATMENT

Although we predicted this lesion to show massive submucosal invasion based on the optical diagnosis using endocytoscopy, we performed endoscopic mucosal resection as the first-line treatment. We decided to determine the need for additional surgery on the basis of the final histopathological diagnosis of the resected specimens.

## OUTCOME AND FOLLOW-UP

Histopathological findings revealed tubular adenocarcinoma (depression) with adenoma (flat area), which was consistent with the results of the endocytoscopic diagnosis. Non-neoplastic glands were observed between the left and right sides. This lesion may have two different origins, that is, the depression and flat areas may correspond to submucosal invasive (T1) cancer and adenoma, respectively. The final histological diagnosis was as follows: Adenocarcinoma (well to moderately differentiated tubular adenocarcinoma) with adenoma, with a depth of invasion of 2407  $\mu\text{m}$  (T1), negative for lymphovascular invasion, budding grade 1, and negative horizontal and vertical margins. He did not wish to undergo additional surgery. In conformity with the Japanese guidelines for the treatment of colorectal cancer, he was followed up using CT, colonoscopy and tumor marker<sup>[7]</sup>. There has not been any



**Figure 3** Final histological diagnosis: Adenocarcinoma (well to moderately differentiated tubular adenocarcinoma) with adenoma, with 2407  $\mu$ m depth of invasion (T1); negative for lymphovascular invasion, grade 1 budding, and negative horizontal and vertical margins.

evidence of recurrence to date.

## DISCUSSION

Several studies have reported the effectiveness of optical diagnosis with endocytoscopy for determining the treatment course of colorectal lesions. Kudo *et al*<sup>[8]</sup> reported that endocytoscopy provided additional diagnostic value to conventional pit pattern classification for colorectal neoplasms. The diagnostic ability of endocytoscopy to predict neoplastic changes was excellent [sensitivity: 97.4%, 95% confidence interval (CI): 95.4%-98.6%, specificity: 89.7%, 95%CI: 78.8%-96.1%, accuracy: 96.5%, 95%CI: 94.5%-97.9%]. In addition, its ability to differentiate massively invasive submucosal colorectal cancer was also good, showing 83.1% (95%CI: 73.7%-90.2%) of sensitivity, 99.1% (95%CI: 97.6%-99.7%) and 96.3% (95%CI: 94.3%-97.8%). Thus, endocytoscopy enables the optical diagnosis of colorectal lesions with high confidence levels. In the present case, we could predict the differences in histopathology between T1 cancer and adenoma within the same lesion by using endocytoscopy in real time.

The histopathological diagnosis of this lesion was T1 sigmoid cancer with adenoma. T1 colorectal cancer accounts for approximately 10% of all LNM; hence, such lesions require additional surgery with lymph node dissection after endoscopic resection for achieving complete cure<sup>[9-12]</sup>. Although several guidelines are available for the management of T1 colorectal cancer after endoscopic resection, the criteria for additional surgery remain controversial<sup>[7,13-16]</sup>. According to the Japanese guidelines, this patient had one risk factor, namely, a depth of invasion  $\geq 1000$   $\mu$ m, and hence, additional surgery was recommended. However, some studies reported that the depth of invasion was not a risk factor for LNM in T1 colorectal cancer<sup>[12,17,18]</sup>. Moreover, the incidence of LNM is extremely low – 1.3% (95%CI: 0%-2.4%) – in the cases with submucosal invasion depth of 1000  $\mu$ m or more without associated risk factors (other than the depth of invasion) as per Japanese guidelines<sup>[7]</sup>. The risk was very low since this patient had no evidence of lymphovascular invasion, reported to have most predictive value<sup>[9]</sup>, differentiation, and tumor budding. However if the lesion recurs, it can be life-threatening; therefore, a decision on additional treatment should be carefully made. This patient refused to undergo surgery 4 years previously despite receiving a clear explanation about the risk of LNM and the merits and demerits of additional surgery. Our findings suggest the need for developing a more accurate risk stratification for LNM in the future.

## CONCLUSION

Endocytoscopy is an effective modality for the optical diagnosis of colorectal lesions. In the present case, we could diagnose the T1 cancer and adenoma components within the same lesion before treatment.



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## Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review

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### Abstract

#### BACKGROUND

Situs inversus totalis (SIT) is a rare anomaly in which structures are located opposite to their usual positions. It is not a premalignant condition and the association with colorectal cancer (CRC) is rare. We here report a patient with SIT who underwent laparoscopic radical resection of sigmoid colon cancer, and review the pertinent literature.

#### CASE SUMMARY

A 53-year-old woman presented with CRC and SIT and underwent a complete examination after admission. The patient then underwent laparoscopic radical resection of sigmoid colon cancer and hyperthermic intraperitoneal chemotherapy. The operation duration was 120 min, and no intraoperative complications occurred. The final pathological report showed stage T4aN0M0. Postoperative chemotherapy was administered and no evidence of recurrence was observed during 18 mo of follow-up.

#### CONCLUSION

Surgery in a patient with CRC and SIT can be safely performed on the basis of routine preoperative clinical examination.

**Key Words:** Colorectal cancer; Situs inversus totalis; Hyperthermic intraperitoneal chemotherapy; Case report

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**Core Tip:** Situs inversus totalis is a rare anomaly in which structures are located opposite to

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their usual positions. It is not a premalignant condition and the association with colorectal cancer is rare. We here report a case and review the literature. In sum, a 53-year-old woman presented with colorectal cancer and situs inversus totalis and underwent a complete examination after admission. The patient then underwent laparoscopic radical resection of sigmoid colon cancer and hyperthermic intraperitoneal chemotherapy. The final pathological report showed stage T4aN0M0. Postoperative chemotherapy was administered and no evidence of recurrence was observed during 18 mo of follow-up.

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## INTRODUCTION

Situs inversus totalis (SIT) refers to the complete reversal of unpaired tissues and organs in the thoracic and abdominal cavity. It is an extremely rare congenital disease with an incidence of approximately 1/4000-8000<sup>[1]</sup>. According to statistics, the incidence of intestinal cancer is about 376.3/100000, and patients with intestinal cancer and visceral transposition are even rare. When lesions of internal organs in the reverse position occur, patients are easily misdiagnosed if imaging data are not available. We here report a patient with complete visceral transposition combined with sigmoid colon cancer. To the best of our knowledge, this is the first case report of sigmoid colon cancer associated with SIT in China. We also review the relevant literature and discuss the diagnosis and treatment of this patient.

## CASE PRESENTATION

### Chief complaints

In December 2017, a 53-year-old woman was admitted to our hospital due to lower abdominal discomfort for 1 wk.

### History of present illness

The patient's symptoms started a week ago with recurrent lower abdominal discomfort, which had been worsened the last 24 h.

### History of past illness

The patient had a free previous medical history.

### Physical examination

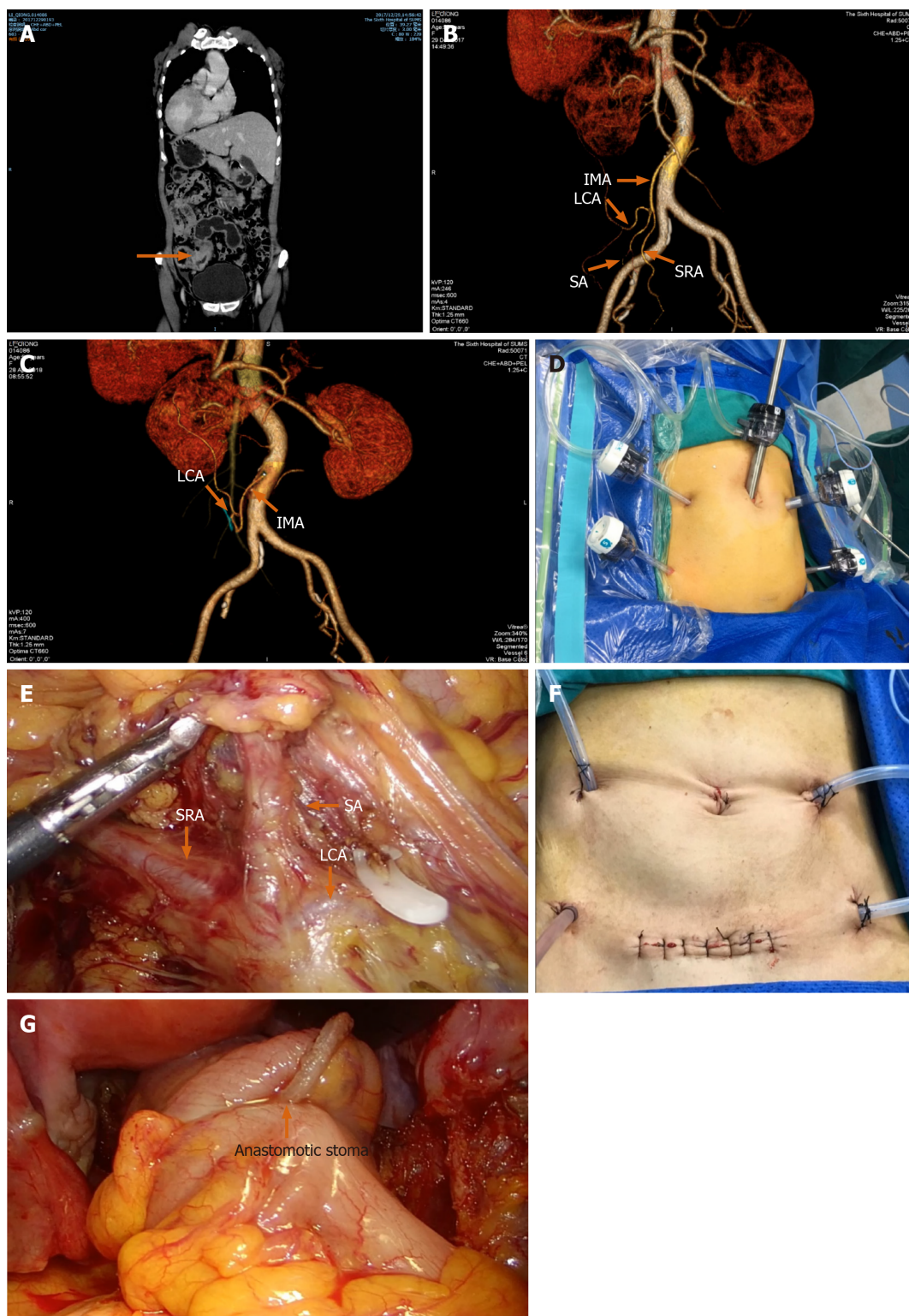
Initial vital signs were stable, and a systemic review and physical examination revealed nothing of note. However, the apex beat of her heart was located in the fifth intercostal space of the right clavicle midline.

### Laboratory examinations

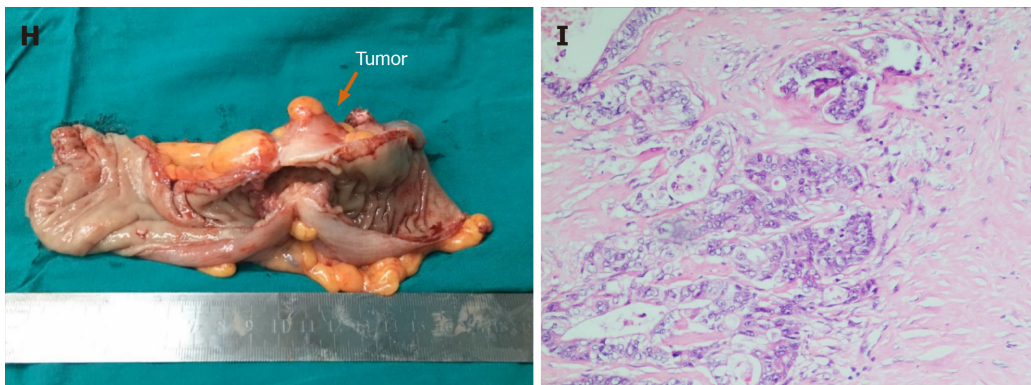
Serum carcinoembryonic antigen level was elevated (68.5 ng/mL; reference range, 0-5.0 ng/mL).

### Imaging examinations

Colonoscopy revealed an obstructing sigmoid mass. Histological examination of the biopsied specimen indicated a moderately differentiated adenocarcinoma. Preoperative thoracic and abdominal enhanced computed tomography showed a complete right-left reversal of the thoracic and abdominal organs, sigmoid colon wall thickening, and the surrounding mesentery scattered with lymph nodes around the primary tumor (Figure 1A). A three-dimensional vascular reconstruction technique was used to observe the anatomy and variation of mesenteric vessels, and the anatomy of the vascular arch was clearly displayed (Figure 1B and C).







**Figure 1 Images of computed tomography, operation, and histopathological examination.** A: Computed tomography showing transposition of the abdominal; B: Three-dimensional reconstruction image of computed tomography angiography showing three branches of the inferior mesenteric artery, left colic artery, sigmoid artery, and superior rectal artery; C: Postoperative three-dimensional reconstruction of computed tomography angiography; D: Sites of trocar placement. A camera was inserted into the subumbilical area through a 12-mm trocar; the 12-mm trocar marked indicates the main operation hole; E: Exposure of each blood vessel during operation; F: The anastomotic stoma; G: Placement of a perfusion tube for hyperthermic intraperitoneal chemotherapy; H: Resected specimen showing a ulcerated mass in sigmoid colon; I: Histopathological examination. IMA: Inferior mesenteric artery; LCA: Left colic artery; SA: Sigmoid artery; SRA: Superior rectal artery.

## FINAL DIAGNOSIS

The final diagnosis was CRC with SIT.

## TREATMENT

On January 5, 2018, under general anesthesia, laparoscopic radical sigmoidectomy was performed and hyperthermic intraperitoneal chemotherapy was administered twice (Figure 1D and G). The surgical method of low ligation in combination with highly selective lymph node dissection was adopted to preserve the left colic artery in order to lower the postoperative incidence of anastomotic fistula. Postoperative pathological staging was T4aN0M0 based on the criteria proposed by the International Union Against Cancer (Figure 1H and I).

## OUTCOME AND FOLLOW-UP

The patient recovered well after surgery, and regular chemotherapy (mFOLFOX6) was performed 8 times. During the regular 18 mo of follow-up, no tumor recurrence was observed and the patient's general condition was good.

## DISCUSSION

We searched the compact disc read-only memory database of Chinese biomedical literature and the PubMed-indexed for MEDLINE search system to retrieve reports on visceral transposition combined with intestinal cancer published from January 2000 to May 2019. The Chinese search terms used were “visceral transposition” and “intestinal cancer”, and the English search terms used were “colorectal cancer” and “situs inversus”. Finally, 2 Chinese articles and 11 English articles were identified (Table 1)<sup>[1-13]</sup>.

Visceral transposition can be divided into complete visceral transposition and partial visceral transposition. Patients with complete visceral transposition are known as “mirror people” and are extremely rare<sup>[14]</sup>. Some patients with visceral transposition often present with other complex malformations. The incidence of visceral transposition varies in different regions. In Japan, the incidence of visceral transposition is 0.125‰ to 0.250‰. Yang *et al*<sup>[15]</sup> reported that the incidence rate was 0.005‰ to 0.010‰ in China. Several reports of the combination of a malignant tumor and SIT, such as cancer of the liver, stomach, lung, and colon, have been described. Only 2 cases of laparoscopy-assisted resection of CRC have been reported in China<sup>[2,3]</sup>.



**Table 1 Summary of cases with complete transposition of viscera combined with intestinal cancer**

Ref.	Publication time	Number of examples	Sex/Age (yr)	Tumor location	Pathological examination	Therapy	Prognosis
Fang <i>et al</i> <sup>[2]</sup>	2014	1	Female/39	Rectum	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Xu <i>et al</i> <sup>[3]</sup>	2018	1	Female/67	Colon ascendens	Medium-poor differentiated adenocarcinoma	Laparoscopic surgery	Good
Takeda <i>et al</i> <sup>[4]</sup>	2018	1	Female/72	Colon sigmoideum	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Sasaki <i>et al</i> <sup>[5]</sup>	2017	1	Female/75	Colon ascendens	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Yaegashi <i>et al</i> <sup>[6]</sup>	2015	1	Female/71	Colon sigmoideum	Well differentiated adenocarcinoma	Laparoscopic surgery	Good
Ito <i>et al</i> <sup>[7]</sup>	2015	2	Female/53; Male/60	Rectum Ascending colon cancer	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Hirano <i>et al</i> <sup>[8]</sup>	2015	1	Male/87	Carcinoma of the cecum	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Sumi <i>et al</i> <sup>[9]</sup>	2013	1	Male/83	Carcinoma of the descending colon	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Kim <i>et al</i> <sup>[10]</sup>	2011	1	Male/63; Female/71	Colon cancer of the hepatic flexure	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Han <i>et al</i> <sup>[11]</sup>	2011	1	Male/63	Ascending colon cancer	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Fujiwara <i>et al</i> <sup>[12]</sup>	2007	1	Female/53	Ascending colon cancer	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Goi <i>et al</i> <sup>[13]</sup>	2003	1	Female/72	Ascending colon cancer	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good
Viscott <i>et al</i> <sup>[14]</sup>	2011	1	Female/71	Rectal carcinoma gastric cancer	Moderately differentiated adenocarcinoma	Laparoscopic surgery	Good

The patient described here had sigmoid colon cancer and underwent laparoscopic radical surgery and postoperative intraperitoneal hyperthermic perfusion chemotherapy. The procedure was uneventful, and no tumor recurrence was found after 18 mo of follow-up.

To date, the mechanism of visceral translocation is still unclear, and some scholars believe that it is related to fetal ectopic and chromosomal abnormalities during embryonic development<sup>[16]</sup>. Whether internal visceral translocation is related to tumor onset is still inconclusive. Studies have shown that there may be a correlation between internal visceral translocation and tumor onset; however, further research is needed<sup>[17]</sup>. Due to the different pathological types and tumor sites, the clinical manifestations of patients vary, especially in patients with visceral transposition, which is prone to misdiagnosis. Therefore, comprehensive examinations should be completed, such as gastrointestinal endoscopy, computed tomography, and revascularization.

As internal visceral transposition is often accompanied by congenital anatomic abnormalities, surgery can be challenging. The main difficulty is distinguishing the blood vessels. In this case, the main branch vessels supplying the intestine were clearly distinguished by revascularization before surgery, which provided a guarantee for a smooth surgical procedure. In addition, it is necessary to consider the handedness of the surgeon to determine the position of the device, operator, and trocars. Oms and other researchers have found that laparoscopic techniques in visceral transposition patients are more difficult for right-handed surgeons, and are more advantageous for left-handed surgeons<sup>[18]</sup>. The same effect can be achieved by changing the position of the operator during surgery<sup>[6]</sup>.

For the diagnosis and treatment of patients with visceral transposition combined with gastrointestinal cancer, the possibility of visceral inversion should always be considered. The presence of cardiopulmonary disease should be eliminated to ensure a smooth surgical procedure. Relevant imaging examinations should be improved, and if necessary, revascularization should be performed to determine whether there are obvious vascular variations. An understanding of the anatomical location and variation involved in the operation is essential, and research on the surgical approach

and possible problems during surgery should be conducted. Compared with traditional laparotomy, laparoscopic techniques have minimally invasive benefits for patients while also presenting challenges. With the continuous development of technology, there will be a further understanding of the diagnosis and treatment of patients with visceral transposition, especially those with tumor diseases. In addition, because patients with stage T4 are prone to postoperative peritoneal metastasis, hyperthermic intraperitoneal chemotherapy and adjuvant chemotherapy were used to prevent tumor peritoneum relapse<sup>[19]</sup>.

## CONCLUSION

CRC and SIT can be diagnosed according to colonoscopy and imaging examination. Radical resection is the most effective method for treating CRC. A clear diagnosis before surgery can reduce the risk of surgery.

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## Do available data support the widespread adoption of pancreatoscopy guided-lithotripsy?

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### Abstract

Peroral pancreatoscopy (POPS) is a demanding endoscopic procedure that can be used to perform intracanal lithotripsy in obstructing pancreatic stones but the experience is limited. Most stones can be removed successfully by endoscopic retrograde cholangio-pancreatography but patients with large stones require advanced therapeutic approaches, such as extracorporeal shock wave lithotripsy (alone or followed by endoscopic retrograde cholangio-pancreatography), currently the mainstay of treatment. Unfortunately, in about 10% of cases, extracorporeal shock wave lithotripsy can fail; moreover, it is not available in many institutions. For this subgroup of patients, POPS guided-lithotripsy can play a role and have benefits. The most consistent study concerns a retrospective multicenter analysis that enrolled few patients per center. Considering the epidemiological scenario and the scant volume of skilled endoscopists, POPS must be developed in very few high-volume referral centers with standardized pathways and capable of performing multi-modality treatment. In addition, we could reasonably assume that POPS-guided-lithotripsy should be used as rescue therapy in special situations, identifying the ideal candidate who can achieve the maximum clinical result, and carefully balancing risk/benefits ratio.

**Key Words:** Pancreatic stones; Pancreatoscopy guided-lithotripsy; Rescue therapy; Extracorporeal shock wave lithotripsy; Endoscopic retrograde cholangio-pancreatography; Referral centers

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**Core Tip:** In chronic pancreatitis, the goal of treatment is reducing pain by eliminating obstructing pancreatic stones. There are several minimally invasive treatment approaches, such as extracorporeal shock wave lithotripsy and/or endoscopic retrograde cholangio-pancreatography; but where they fail, more advanced therapeutic techniques can be used.

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Peroral pancreatoscopy guided-lithotripsy is an appropriate option but should be performed as rescue therapy by experienced endoscopists in very few high-volume referral centers.

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## TO THE EDITOR

Peroral pancreatoscopy (POPS) is an endoscopic, challenging procedure to directly visualize the main pancreatic duct, permitting tissue acquisition, and can be also used for therapeutic purposes, such as intracanalicular lithotripsy<sup>[1]</sup>. Although in the last decade technology has been continuing to improve with the recent development of single-operator digital cholangio-pancreatography, pancreatic experience is limited.

In chronic pancreatitis, the goal of treatment is reducing pain by eliminating obstructing pancreatic stones. While the use of cholangioscopy for difficult biliary stones' management is well documented, most pancreatic stones (< 5 mm) can be removed successfully by endoscopic retrograde cholangio-pancreatography (commonly known as ERCP). Patients with large stones require advanced therapeutic approaches, such as extracorporeal shock wave lithotripsy (ESWL) (alone or followed by ERCP), currently the mainstay of treatment. Unfortunately, in about 10% of cases, ESWL can fail or not be suitable; moreover, it is not available in many institutions. In this subgroup of patients, POPS guided-lithotripsy (POPS-gl) can play a role and have benefits.

"Extrema ratio" surgery offers the best long-term results for chronic pancreatitis, being associated with a lower rate of relapse<sup>[2]</sup>; although, the biggest criticism of any study is that neither ESWL nor POPS-gl was included in the endoscopic arm. We must keep in mind that not all endoscopists performing cholangioscopy routinely have dexterity in direct intraluminal lithotripsy for difficult biliary stones' treatment. This further restricts the field of endoscopist experts. Nowadays, if you look at the available literature, you realize the low volume of patients treated and that data must be interpreted with caution.

The most consistent study concerns a retrospective analysis involving 17 centers in the United States and Europe, where just over 100 cases (about 6 patients per center!) treated with POPS-gl were enrolled during 3 years<sup>[3]</sup>. In others published reports, describing a systematic review<sup>[4]</sup> and a retrospective multicenter cohort<sup>[5]</sup>, the authors collected a total of 87 and 28 patients, respectively. From all these data, the scant volume of skilled endoscopists and the epidemiological scenario, we believe POPS must be developed in very few high-volume referral centers with standardized pathways and capable of performing multi-modality treatment.

In addition, we could reasonably assume that POPS-gl should be used as rescue therapy in special situations and will be associated fewer interventions, more wide de-obstructions and lower risk of infection. Thus, it seems wise to implement a new level of evidence in order to identify the ideal candidate who can achieve the maximum clinical result, while carefully balancing risk/benefits ratio.

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## Comment on: Should a colonoscopy be offered routinely to patients with CT proven acute diverticulitis? A retrospective cohort study and meta-analysis of best available evidence

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### Abstract

Latest evidence indicates that patients with acute diverticulitis have higher prevalence of colorectal cancer than reference patients. Therefore, colonoscopy should be offered after an episode of acute diverticulitis.

**Key Words:** Colorectal cancer; Adenoma; Polyp; Diverticulitis; Colonoscopy; Endoscopy

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**Core Tip:** In a recent meta-analysis, we reported higher prevalences of polyp, adenoma, advanced adenoma and colorectal cancer in patients with diverticulitis than the prevalences reported by Asaad *et al.* Further, evidence indicates that the 1-year incidence of colorectal cancer is higher in patients with diverticulitis than in reference patients. Therefore, we believe that colonoscopy should be offered after an episode of diverticulitis, in opposition with the conclusion reached by the authors.

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## TO THE EDITOR

We thank Asaad *et al*<sup>[1]</sup> for their interesting publication in the field of colorectal cancer and diverticulitis, that we have read with great attention.

The authors questioned the recommendations of the Association of Coloproctologists of Great Britain and Ireland and the American Society of Colon and Rectal Surgeons to perform a colonoscopy after an episode of acute diverticulitis. To this end, the authors compared the prevalences of polyp, hyperplastic polyp, adenoma, non-advanced adenoma, advanced adenoma and colorectal cancer in 68 patients undergoing colonoscopy after an episode of diverticulitis with the prevalences in 1309 asymptomatic patients undergoing screening colonoscopy.

In patients with diverticulitis, they reported the following prevalences: Polyp 16.2%, hyperplastic polyp 8.8%, adenoma 5.9%, non-advanced adenoma 5.9%, advanced adenoma 0% and colorectal cancer 0%. These prevalences were not significantly different from those found in patients undergoing screening colonoscopy. Then, to support their results, the authors performed a systematic review and meta-analysis of the literature (searching MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, clinicaltrials.gov and the ISTCTN register), including three retrospective cohort studies comparing the prevalences of adenomas and neoplasms between patients with and without diverticulitis, in addition to their own study which they included in the quantitative analysis. Again, the authors described that the pooled risk differences between patients with and without diverticulitis were not different for polyp, adenoma, non-advanced adenoma, advanced adenoma and colorectal cancer.

Asaad *et al*<sup>[1]</sup> concluded that “*routine endoscopy assessment of patients after an episode of CT proven acute diverticulitis may be unnecessary*”. The authors proposed endoscopy to be performed on a “*case-by-case basis*” and to reserve it to patients with complicated diverticulitis.

However, we believe that the authors are drawing hasty conclusions that are not supported by the literature in the field. For instance, in a recent systematic review and meta-analysis pooling 31 studies representing 50445 patients, we showed that the prevalence of colorectal cancer was 1.9% (95%CI: 1.5%-2.3%) in patients with diverticulitis. When only considering patients who underwent endoscopy (12 studies), that prevalence was 2.3% (95%CI: 1.4%-3.7%). Further, we reported the following prevalences for polyps: Polyp 22.7% (21 studies, 95%CI: 19.6%-16.0%), hyperplastic polyp 9.2% (13 studies, 95%CI: 7.6%-11.2%), adenoma 14.2% (15 studies, 95%CI: 11.8%-17.1%) and advanced adenoma 4.4% (8 studies, 95%CI: 3.4%-5.8%)<sup>[2,3]</sup>. We note that these prevalences are higher than the prevalence reported by Asaad *et al*<sup>[1]</sup> in patients suffering from diverticulitis.

In our meta-analysis, we did not compare our reported prevalences to the ones from a reference population. However, in a retrospective cohort study including 506 patients with CT-proven episode of acute diverticulitis, and comparing the 1-year incidence of colorectal cancer in that population with the incidence in an age- and gender-matched population, we have shown that the incidence of colorectal cancer in patients with diverticulitis was 44-fold higher (standardized incidence ratio, 95%CI: 18.58-75.96) than in the reference population. This was observed in patients with uncomplicated episode as well as in those with complicated episode<sup>[4]</sup>. These findings were later confirmed by other teams<sup>[5,6]</sup>.

Therefore, we believe that patients with diverticulitis should be offered colonoscopy to exclude neoplastic lesions<sup>[7,8]</sup>.

We think that the opposing conclusions reached by Asaad *et al*<sup>[1]</sup> might be explained by limitations in their study design, as they have reported in their publication. First, we believe that the number of patients suffering from diverticulitis included by the authors over a three-year period in three centers is too small and that their study is insufficiently powered to show any difference with reference patients. Further, details regarding included patients (inpatients/outpatients, uncomplicated/complicated diverticulitis) were not reported. This is of importance as patients with complicated episode, for instance, were documented to have higher incidence of colorectal cancer<sup>[2]</sup>. Moreover, patients from the control group were part of the National Bowel Cancer Screening Program, which consisted in the guaiac fecal occult blood test (now replaced by the fecal immunochemical test)<sup>[9]</sup>. The objective of this program is to offer endoscopic screening to patients with higher probability of colorectal lesion identified by a positive fecal test. Therefore, we believe that the reference population used by Asaad *et al*<sup>[1]</sup> was not adequate and led to an overestimation of the prevalence of neoplastic lesions in control patients.

To conclude, we think that the conclusions reached by Asaad *et al*<sup>[1]</sup> should not lead

to a change of practice regarding the indication for colonoscopy after an episode of diverticulitis.

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