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REVIEW

Foreign object ingestion and esophageal food impaction: An update and review on endoscopic management

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Abstract

Foreign body ingestion encompasses both foreign object ingestion (FOI) and esophageal food impaction (EFI) and represents a common and clinically significant scenario among patients of all ages. The immediate risk to the patient ranges from negligible to life-threatening, depending on the ingested substance, its location, patient fitness, and time to appropriate therapy. This article reviews the FOI and EFI literature and highlights important considerations and implications for pediatric and adult patients as well as their providers. Where published literature is insufficient to provide evidence-based guidance, expert opinion is included to supplement the content of this comprehensive review.

Key words: Foreign bodies; Endoscopy; Gastrointestinal emergency; Medical management; Dysphagia

Core tip: Foreign body ingestion encompasses both foreign object ingestion (FOI) and esophageal food impaction (EFI) and represents a common and clinically significant scenario among patients of all ages. This article reviews the FOI and EFI literature and highlights important considerations and implications for pediatric and adult patients as well as their providers.

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INTRODUCTION

Foreign body ingestion is a common and potentially life-threatening clinical problem with an estimated annual incidence of 120000 cases in the United States alone[1]. The majority of these cases occur in children as a result of curiosity and accidental ingestion, with peak incidence occurring between the ages of 6 mo and 3 years[2]. In adults, groups at higher risk include those with severe psychiatric disorders, mental retardation, acute intoxication, or seeking secondary gain (*e.g.*, incarcerated individuals seeking transfer out of prison to a medical facility)[3-5]. Although the majority of ingested foreign bodies will traverse the gastrointestinal (GI) tract uneventfully, 10-20% will require intervention, most often endoscopic, to mitigate complications such as impaction, ulceration, perforation, and potentially death[6-9]. These complications preferentially occur at areas of physiologic or pathologic sharp angulation or narrowing (Figure 1) and appear to be more common and associated with relatively higher morbidity in intentional as compared to accidental ingestion[3,10-12].

Foreign body ingestion can be classified into two main groups: true foreign object ingestion (FOI) and esophageal food impaction (EFI). These groups encompass a wide variety of potentially ingested substrates, making every case a new potential challenge for even highly experienced gastroenterologists. Furthermore, there is considerable geographic variation in the epidemiology of FOI, both in terms of the ingested substrate as well as the patient demographic. For example, in the United States, food (meat) impaction is the most common FOI in adults[13,14], and eosinophilic esophagitis has become recognized as an increasingly common underlying diagnosis (Table 1)[14-16]. In contrast, bones (primarily fish) represent the most common foreign body ingestions in Spain[17], Iran[18], Nigeria[19], Ethiopia[20], India[21], and China[22,23]. These patterns are different, however, among pediatric patients (where FOI, *e.g.*, coin ingestion, is more common)[2,24-27] and elderly patients (where dental prosthesis ingestion is more common) both in the United States as well as globally[22]. Given the heterogeneity in types of foreign bodies (Table 2) and in demographic characteristics, clinical presentation can vary between cases, as can the array and likelihood of complications. Accordingly, management requires careful diagnosis, recognition of the potential risks, and planning for appropriate intervention.

As GI endoscopy has become the method of choice for the management of most FOIs and EFIs, it is critically important for gastroenterologists to understand the role and timing of endoscopic intervention as well as the tools for proper therapy in order to avoid complications and mitigate potential morbidity. Therefore, this review will summarize available evidence that should be considered when managing FOI and EFI and provide diagnostic and therapeutic algorithms for clinicians involved in the care of these patients. Where evidence is limited, we suggest pragmatic approaches based on current data, clinical experience, and expert opinion.

GENERAL PRINCIPLES OF MANAGEMENT

Diagnosis

History and physical examination: In most adults and older children, FOI and EFI are often recognized at the time of the incident, and the history, including the material swallowed and location of discomfort, can be obtained from the patient. In younger children and the psychiatrically (or otherwise mentally) impaired, diagnosis often becomes more challenging, especially when an episode is unwitnessed. Importantly, the site of discomfort or other symptomatology (if present) often does not reliably predict the location of pathology, especially when occurring below the cricopharyngeus[28]; for example, distal esophageal impaction related to an underlying peptic stricture may be referred to the throat region.

The presentation of FOI depends greatly on the nature of the ingested material, anatomical factors (*e.g.*, prior surgery), and the time that has elapsed from initial

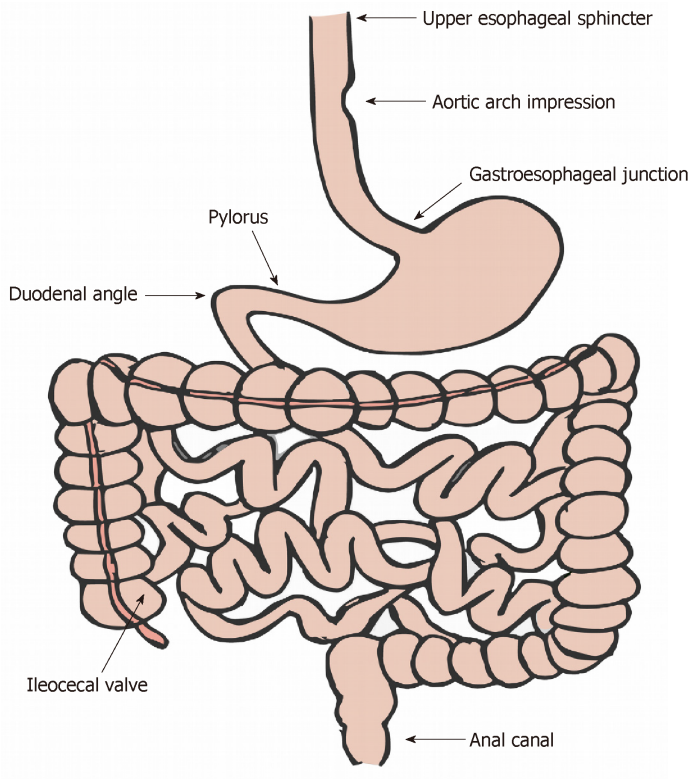

Figure 1 Areas of acute angulation and narrowing (physiologic or pathologic) in the gastrointestinal tract. The areas depicted represent sites of potential food or foreign object impaction.

ingestion. Presenting symptoms may include choking, refusing to eat, vomiting, abdominal pain, respiratory distress (particularly in pediatric patients with proximal esophageal FOI or EFI), or blood-tinged saliva, among others[29-32]. Thus, a careful history (*e.g.*, regarding the ingested material, prior history of dysphagia/similar episodes, the use of removable dental hardware, and prior GI surgeries) obtained from the patient and/or witnesses is essential and may provide critical diagnostic clues.

With regard to EFI, the classic presentation consists of acute onset substernal chest pain/discomfort and difficulty swallowing while eating boneless (typically roasted or pulled) pork, beef, or poultry due to a sensation that food is "getting stuck". In some cases, the presentation may be more insidious, and often times patients frequently will not present until several hours after symptom onset, hoping that symptoms will resolve spontaneously with time. In addition to chest pain and dysphagia, other commonly reported symptoms include foreign body sensation, odynophagia, sialorrhea, and a need to spit up secretions. When obtaining a history, it is important to inquire about the content of recent meals and assess whether the ingesta was boneless or if it may have contained bones, as this could change the management approach and the spectrum of potential sequelae.

The physical examination in patients with suspected FOI or EFI should involve evaluating for evidence of luminal obstruction and other complications, especially perforation (which may manifest, for example, with cervical swelling and/or crepitus in the case of oropharyngeal/proximal esophageal perforation, or with fever and peritonitis in the case of intestinal perforation).

Imaging and localization: Assessment of the anatomic location is of central importance in the clinical management of FOI and EFI. Imaging studies can provide valuable information on the location as well as the morphology and nature (*e.g.*, size and sharpness, composition, and number of objects) of the foreign body. Fortunately, most FOIs are composed of radiopaque material and can be identified on projectional X-rays (*e.g.*, posterior-anterior and lateral images) of the neck, chest, or abdomen. However, objects such as thin bones, plastic, glass, and wood may not be readily seen. X-rays can also provide useful information regarding possible aspiration and free mediastinal or peritoneal air[33]. Contrast administration should generally be avoided given the risk and potential complications of contrast aspiration[6]; moreover, contrast coating of the foreign body and esophageal mucosa can compromise subsequent

Table 1 Underlying disorders in esophageal food impaction

Eosinophilic esophagitis
Schatzki's ring
Peptic stricture
Radiation-induced stricture
Esophageal carcinoma
Zenker's diverticulum
Non-Zenker's esophageal diverticulum
Post-surgical (*e.g.*, fundoplication)
Achalasia
Other spastic dysmotility

Upon further evaluation, many patients with esophageal food impaction are found to have one or more of these disorders.

endoscopy[29,34]. Computed tomography (CT) scanning may be useful (Figure 2)[35-38], particularly if complications are suspected[9], and its sensitivity and accuracy can be improved with three-dimensional reconstruction[39]. Handheld metal detectors can be useful in metallic FOI, particularly in pediatric patients, as well as in the detection of certain radiolucent metallic foreign bodies like aluminum[40-44]. Additional details regarding initial noninvasive diagnostic as well as elimination follow-up imaging have been discussed in recent radiology society clinical guidelines[45].

In the setting of a negative radiographic evaluation but suspected foreign body ingestion and persistent esophageal symptoms, endoscopic intervention is warranted[29,46]. In addition, patients with suspected non-bony EFI without complications (*e.g.*, no evidence of perforation or respiratory distress) can proceed to endoscopic evaluation without obtaining radiographs[6,9].

Preparation and planning

Airway management: Initial management of patients with FOI and EFI includes assessment of ventilatory status and airway protection. Most adult cases of FOI and EFI may be managed with moderate sedation. In the presence of wheezing, stridor, or dyspnea, however, emergent endotracheal intubation may be indicated. Similarly, endotracheal intubation is appropriate for facilitating airway protection in patients who are unable to manage their secretions (*e.g.*, due to very proximal EFI) and are thus at high aspiration risk[9]. Endotracheal intubation may likewise be indicated for patients with FOI or EFI that is difficult to remove and in cases with multiple objects requiring removal. An overtube may be used to provide additional airway protection, and these are discussed in a forthcoming section[9]. Notably, pediatric GI endoscopy often requires general endotracheal anesthesia, in part due to the fact that smaller and more compliant airways have a higher risk of airway obstruction during endoscopy[46].

Timing and urgency of intervention: Once FOI or EFI is diagnosed, the provider must decide whether intervention is necessary, and if so, how urgently intervention is required. The need for and timing of an intervention for FOI and EFI are dependent on multiple factors; these include patient age and clinical condition, the location and characteristics of the ingested material (Table 2), time since ingestion, and the technical capabilities of the endoscopist and facility[47]. Based on these factors and the perceived risks of aspiration, obstruction, perforation, and other potential complications, as well as the likelihood of procedural success, the timing and nature of endoscopic intervention is determined. As stated previously, patients unable to effectively manage their secretions (*e.g.*, due to complete esophageal obstruction from EFI) or with sharp or disk battery FOI require emergent endoscopic intervention (preferably within 2 h, and at the latest within 6 h)[9]. Other scenarios (*e.g.*, asymptomatic blunt foreign object in the esophagus or incompletely obstructing EFI) need not be managed emergently but should undergo endoscopic intervention within 24 h as delay beyond this time interval decreases the likelihood of successful removal and increases the risk of complications, including but not limited to perforation[48-50]. In cases of FOI where the object has made it past the esophagus, most patients who are clinically stable, in no acute distress, and without signs of GI obstruction will not require urgent endoscopy as the ingested object will often pass spontaneously[3,6,51]. For such patients, conservative outpatient management is reasonable[9,52,53], although endoscopic removal may also be appropriate depending on the circumstance (*e.g.*, disk and cylindrical batteries in the stomach that have not progressed in 48 h),

Table 2 Classification of ingested foreign objects

Size
Length (≤ 5 *vs* > 5 cm) Width (≤ 2 *vs* > 2 cm)
Surface consistency
Sharp/pointed *vs* blunt
Smooth *vs* rough/traumatic
Material
Food (boneless *vs* with bone)
Battery
Magnet
Packaged drugs
Chemical/physical characteristics
Radiodensity
Metallic *vs* non-metallic
Chemical reactivity/inertness

A clinically practical classification system for ingested foreign objects. Variations (*e.g.*, in size categories) may exist in specific scenarios.

especially given the high success rate and low risk of adverse events in the majority of cases[6,22,54,55]. If endoscopy is foregone, patients may resume a regular diet but should monitor their stool for passage of the ingested object. In the absence of symptoms, weekly imaging (*e.g.*, X-rays, depending on the type of FOI) should be obtained to follow the progression of small blunt objects that have not yet passed in order to ensure their passage. Specific clinical circumstances are discussed in forthcoming sections.

When to avoid endoscopic intervention: As mentioned above, endoscopy can be foregone in cases where patients are asymptomatic and spontaneous passage is believed to be likely. Special note should be made of the importance of avoiding endoscopic intervention in cases of internal concealment of illicit drugs (*i.e.*, "body packers" or "drug mules"). Here, multiple packets of contraband are typically swallowed and pose a risk for obstruction or rupture. Endoscopic removal should generally not be attempted because of the high risk of rupturing a packet, which can lead to fatal drug overdose. Therefore, these patients should be managed conservatively with close monitoring, serial imaging, and assessments for potential toxicity; surgical intervention may be indicated should removal become necessary[8].

Therapeutic equipment and supplies

Endoscopes: Most FOIs and EFIs are best treated with flexible endoscopes[6,56]. This approach has a high success rate, is generally safer than rigid endoscopy[57], and can be performed with moderate sedation in a majority of cases. However, in some instances, rigid esophagoscopy may be preferable, *e.g.*, for proximal FOIs and EFIs impacted at the level of the upper esophageal sphincter or hypopharynx (*i.e.*, above the cricoid cartilage)[17,54,57-59]. Standard or therapeutic endoscopes are preferable, but small-caliber endoscopes may be used (*e.g.*, if a transnasal approach is deemed necessary or if the patient is unfit for sedation)[60]. However, based on randomized controlled trial (RCT) data, cases of small-caliber endoscope failures can frequently be successfully treated with a standard endoscope, whereas the converse does not appear to be true[61]. Recently, single- and double-balloon enteroscopes are being used in the management of FOIs which are beyond the reach of conventional endoscopes; this is discussed further below[62-65].

Retrieval devices and accessories: A variety of devices and accessories have been described in the published literature for management of FOI and EFI, including but not limited to rat-tooth and alligator forceps, polypectomy snares, multi-prong graspers, Dormia baskets, Roth retrieval nets, Foley catheters, and variceal ligator caps[66-68]. More recently, the use of balloon dilators[69] and sutures[70] has also been described, as has the use of other accessories[71]. The choice of retrieval device depends largely on the type of FOI or EFI and endoscopist experience and preference[72-74]. Foley catheter techniques have also been described and may be more cost-effective in certain pediatric care scenarios (*e.g.*, coin ingestion)[75,76] but are not often used in the adult population. A recent RCT showed that use of a soft, clear cap at the end of the

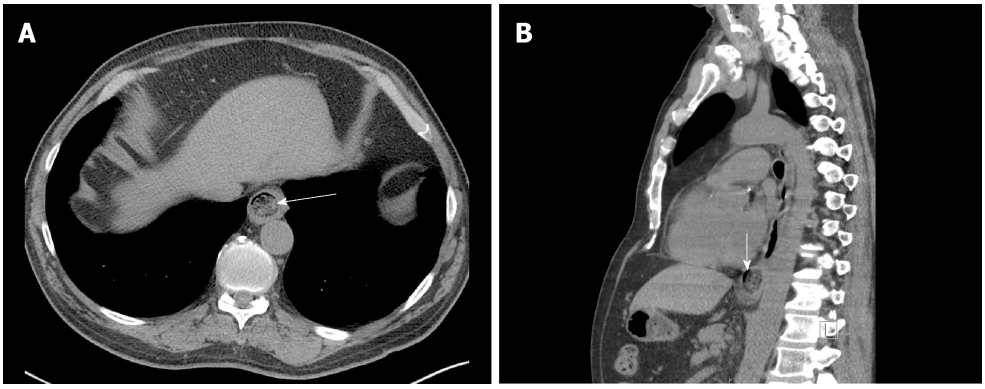

Figure 2 Computed tomography revealing an esophageal food impaction. A: Axial tomogram revealing a food bolus (arrow) in the distal esophagus; B: Sagittal tomogram reveals a sliver of space around the bolus (vertical arrow) suggestive of an opportunity to wedge in the endoscope and employ the push technique or to pass a guidewire (*e.g.*, for the balloon dilation technique).

endoscope may provide an advantage by improving visibility and shortening the procedure time[77]. Regardless of the technique and devices/accessories used, *ex-vivo* practice using the planned retrieval equipment and an object similar to the ingested foreign object can help determine the suitability of the proposed therapeutic approach.

Overtubes: Use of an overtube during the management of FOI and EFI: (1) provides airway protection during retrieval and (2) allows for multiple passes of the endoscope during retrieval, and iii) shields the esophageal mucosa from injury when removing sharp or pointed objects[78,79]. When the object is distal to the esophagus, a longer overtube that extends across the esophagogastric junction can provide additional protection and is often recommended[9]. Overtubes are less commonly used in pediatric patients, as there may be increased risk of esophageal injury and retching associated with overtube insertion. However, newer, softer overtubes may be considered in larger children and adolescents[80].

An alternative to an overtube in cases of sharp or pointed object retrieval is the use of a latex protector hood, which is placed over and affixed to the tip of the endoscope. The bell portion of the protector hood remains inverted during insertion of the endoscope and then flips back to its original shape during withdrawal as it crosses a region of narrowing (*e.g.*, the lower esophageal sphincter)[8,81,82].

Pharmacologic agents: Glucagon has long been employed in the management of EFI and is in fact one of the only interventions to have been studied in the setting of an RCT[83]. The proposed mechanism of action of glucagon in facilitating resolution of EFI involves its spasmolytic activity. Although the aforementioned RCT failed to show therapeutic effects, the study had several notable limitations. For example, it did not specifically investigate whether glucagon could facilitate endoscopic therapy (by facilitating engagement of the impacted bolus via decreasing esophageal spasms), but rather assessed whether it would increase the rate of spontaneous passage. Based on one prospective (non-randomized) study[84], anecdotal experience, and various retrospective series[71,85,86], treatment with glucagon is generally reasonable in the management of patients with EFI[6,29], realizing though that it will be effective in only some patients[9,87]. With respect to dose, esophageal tone appears to reach a nadir at 0.5 mg (based on the results of the only published study of its kind)[88]; however, these data were obtained in normal healthy controls and based on pressure measurements at the lower esophageal sphincter and therefore cannot necessarily be extrapolated to individuals with EFI in a more proximal portion of the esophagus. As a result, and based on its safety and potential usefulness as demonstrated in a prospective (nonrandomized) trial[89], most practitioners advocate for the administration of glucagon 1.0 mg intravenously in cases of EFI prior to endoscopic intervention[6]. If there is no apparent improvement in symptoms and no adverse effects, a repeat dose (within 15-30 min) in an attempt to further relax the esophagus is reasonable, particularly for non-meat EFI, although high quality evidence to support this practice is currently lacking[86].

Effervescent agents such as cola or other carbonated drinks have long been used alone or in combination with other pharmacologic agents (*e.g.*, glucagon)[90-93]. The evidence supporting their use includes a single prospective study[84] and several case series and reports; the collective results suggest that effervescent agents may help to achieve spontaneous resolution of EFI and are associated with little risk in patients

capable of protecting their airway. Therefore, the administration of an effervescent is reasonable in select patients (*e.g.*, who do not appear to have severe impaction), but as with other pharmacologic therapies, should not delay endoscopic intervention[93].

The use of various other agents has been described in the management of EFI but is not routinely recommended for this indication[6,94]. Hyoscine butylbromide (*i.e.*, butylscopolamine), a peripherally acting antimuscarinic, anticholinergic agent, is believed to exert potentially therapeutic effects through its spasmolytic activity (similar to glucagon); its use is supported by very limited published data, none of which are prospective[95-97]. Benzodiazepines have also been employed in patients with EFI[83,98,99]. However, the evidence for their use is sparse, and the literature suggests that they are no more effective than placebo[83]; moreover, there is concern that benzodiazepines may impair a patients alertness and thus airway protection. Lastly, use of proteolytic enzymes (*e.g.*, papain) has been described, but this should be avoided due to numerous associated risks, including esophageal erosion and perforation[8,29,100].

MANAGEMENT OF EFI

The most common EFI in adults in the Western world is impacted meat[8]. Endoscopic treatment options for disimpaction include extraction of the impacted food bolus or advancement of the bolus into the stomach, as discussed below and summarized schematically in Figure 3. Extraction may involve either en bloc or piecemeal removal, depending on the clinical circumstance, using the various accessories and devices as listed above. Radiographic assessment prior to endoscopy is not necessary unless bone fragments are suspected based on the clinical history; if present, these should serve as an alert to the endoscopist, as they may increase complexity of endoscopic treatment. As mentioned earlier, pharmacologic agents are reasonable in an attempt to promote non-invasive passage of the bolus and avoid urgent endoscopy.

Advancement (*i.e.*, pushing) of the bolus into the stomach is the primary means of treating EFI. Prior to doing so, however, the esophagus distal to the obstruction should be examined (by passing the endoscope around the bolus)[9,29,47,71]. The rationale for this lies in the relatively high incidence of underlying esophageal pathology associated with food impactions, thus raising concern for and risk of esophageal perforation[14,15]. Nevertheless, large published series have suggested that the push technique for soft food impaction, when performed by an experienced endoscopist, is both safe and frequently effective[101,102]. In these series, gentle pressure is applied to the middle of the food bolus in an attempt to push the object into the stomach. If this fails, pieces of the bolus are broken off, typically with forceps, followed by a repeat attempt to push the object forward. A balloon dilation technique has been described wherein a guidewire is passed through the food bolus, over which a dilating balloon is passed, inflated in the stomach, and then pulled back through the stricture; once the stricture is dilated, the food bolus is advanced into the stomach[69]. An alternative technique which the authors have recently described involves burning through a food bolus with a bipolar coagulation probe followed by securing the food bolus with opening of an Ovesco triprong anchor in the burn defect (Figures 4A-D)[103]. Regardless of the technique(s) chosen for an individual case, disimpaction attempts should not be delayed beyond 12-24 h from symptom onset given the increasing risk of complications with time[29,47,49,104,105]. In addition, and as described earlier, an overtube should be used in situations where a food bolus has become soft and fragmented, thus requiring repeated esophageal intubations, or if there is an increased risk of aspiration without an option for timely general endotracheal anesthesia.

Once food bolus advancement or extraction has been performed, in most circumstances, it is considered beneficial and safe to perform esophageal dilation (if an underlying stricture is found) in order to reduce the risk of recurrent EFI[6,29,71,101,102]. In cases of prolonged EFI, if eosinophilic esophagitis is suspected, or if underlying mucosal trauma is noted, dilation should be deferred to a later date (and often following a course of acid suppression therapy) to minimize the risk of iatrogenic perforation[71,106]. If a stricture or other luminal narrowing is not found, esophageal biopsies should be considered after the EFI has been cleared (*e.g.*, to rule out eosinophilic esophagitis).

MANAGEMENT OF FOI

In the forthcoming subsections, we provide an overview of FOI management based on the type/characteristics of the object, as summarized schematically in Figure 5.

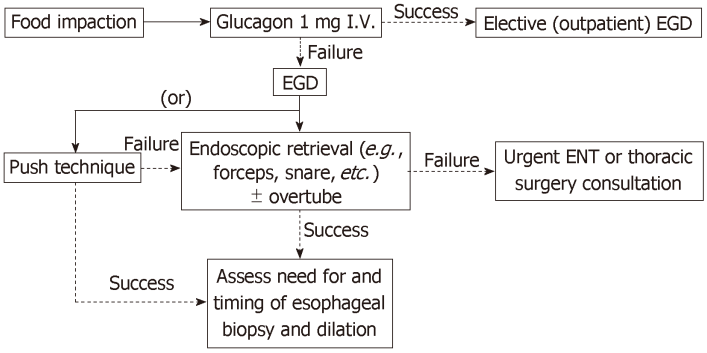

Figure 3 Proposed management algorithm for esophageal food impaction. In the management of esophageal food impaction, the use of glucagon can be first attempted to relax the esophagus and promote spontaneous passage. If unsuccessful, endoscopic retrieval or advancement of the bolus into the stomach can be attempted. EGD: Esophagogastroduodenoscopy; ENT: Ear, nose, and throat (otolaryngology).

Short, blunt objects

FOI involving short, blunt objects such as coins and buttons occurs most often in the pediatric population. When there is suspicion of such FOI in a pediatric patient, X-ray radiographs should be ordered, as impaction in the esophagus may be asymptomatic in a substantial proportion of cases[107]. Coins lodged in the esophagus should be treated with endoscopic retrieval within 12 to 24 h to allow an appropriate pre-anesthetic fast in patients who are asymptomatic[6,80]. In contrast, endoscopic retrieval of coins in the esophagus should be performed emergently in symptomatic patients who are unable to swallow secretions or have acute respiratory symptoms. If more than an hour has elapsed since the last imaging study, imaging should be repeated to confirm that the object is still in the esophagus prior to proceeding with endoscopy. Objects lodged at or above the level of the cricopharyngeus are generally best removed laryngoscopically, while impactions below this level can be removed via flexible upper endoscopy[58,107,108]. If a coin or similar object is found in a patient with several days of symptoms, the possibility of esophageal erosion by the object should be considered, and additional diagnostic evaluation, such as CT imaging, should be performed[37,80].

In adults, endoscopic removal can usually be achieved under moderate sedation, whereas in pediatric patients, general endotracheal anesthesia is typically required, as mentioned earlier[57]. Coins can be easily retrieved with a forceps device (*e.g.*, rat-tooth, alligator) or a snare; smooth, spherical objects are best retrieved with a Roth retrieval net[29,109], as demonstrated in a prospective study[72]. Objects that cannot be readily grasped in the esophagus may be advanced into the stomach to facilitate grasping and retrieval[47]. The use of an overtube with an inner diameter greater than that of the ingested object provides an additional degree of safety, particularly if multiple objects are suspected or present[29]. Alternative techniques, including use of Foley balloon catheters and nasogastric tubes outfitted with magnets, have also been reported (*e.g.*, in cases where endoscopy is not readily available)[110,111], but these approaches generally offer no advantage over or are inferior to endoscopic removal[29,68,112]. The major disadvantage to such techniques is that they provide: (1) minimal control of the object as it is being removed; (2) no airway protection; and (3) no visualization of the esophagus to assess for underlying pathology or complications (*e.g.*, mucosal injury)[47]. Once the ingested (blunt, short) object enters the stomach, conservative outpatient management is usually appropriate[6,9,29], and the majority of objects will pass spontaneously within 4 to 6 d. However, spherical objects > 2.5 centimeters in diameter (or smaller in pediatric patients) are less likely to pass the pylorus, and if retained for > 3-4 wk (or less, depending on composition) or remaining in the same location for > 1 wk, should generally be removed endoscopically[8,29,47,54]. A regular diet can usually be continued while patients monitor their stools for passage of the foreign body. As long as a patient remains asymptomatic, radiographs evaluating the progression of small blunt objects can be performed weekly[8,13]. If symptoms of fever, vomiting, or abdominal pain arise, immediate CT imaging is warranted followed by prompt endoscopic and/or surgical evaluation[3,6,8,29].

Sharp and pointed objects

A myriad of sharp and/or pointed FOIs have been described, and these may be accidental or intentional. In children, most such ingestions are accidental; in adults, sharp bones (*e.g.*, fish, chicken) and toothpicks (Figure 6A-C) are usually ingested

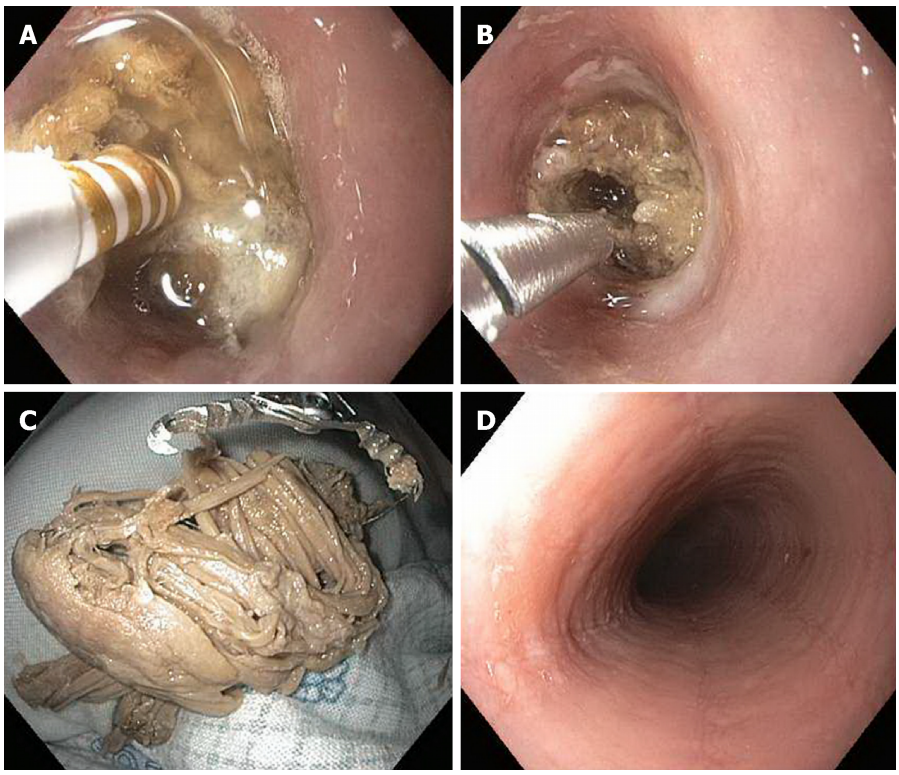

Figure 4 Esophageal food impaction removal. A 48-year-old man in whom attempted extraction of an esophageal food impaction had failed at an outside emergency department was emergently referred to our institution for further management. Endoscopic examination revealed a boneless meat bolus lodged in the mid-esophagus. A: A tract in the center of the bolus was made using a bipolar coagulation probe; B, C: Next, an Ovesco triprong anchor was deployed in the tract (B), and the meat bolus was extracted in one piece (C). D: Mucosal changes including a ringed esophagus, longitudinal furrows, and small-caliber esophagus were found (D), and mucosal biopsies demonstrated evidence of underlying eosinophilic esophagitis[103].

accidentally, whereas most other sharp and/or pointed FOIs (*e.g.*, pins, needles, razorblades, nails, straightened paper clips) are intentional[29,80]. Patients suspected of sharp and/or pointed FOI must be thoroughly evaluated to define the nature, location, and potential complications related to the object. Since many such objects are not readily visible by plain films, CT imaging may be considered in lieu of (and may be more cost-effective than) simple radiographs[35-38,113], and endoscopy should follow a negative radiologic examination to ensure absence or passage of the FOI, or to provide therapy[56].

Sharp and/or pointed FOIs represent a potential medical emergency given their potential for serious complications, with earlier intervention associated with a lower risk of complications[29,105,114,115]. As with other FOIs, sharp objects lodged at or above the cricopharyngeus should be retrieved via direct laryngoscopy, while objects below this area should be retrieved via flexible endoscopy[116]. Objects will generally pass through the GI tract uneventfully once entering the stomach, though the risk of potential complication is not insignificant[13,80]. Therefore, retrieval should be pursued if within safe endoscopic reach (*e.g.*, in the stomach or proximal small bowel)[29,82,117]. Otherwise, these pointed objects, as with others, may be followed with noninvasive imaging studies to document their passage or failure to progress, in which case surgical consultation should be obtained[8,29]. In the interim, patients should be advised to immediately report abdominal pain, persistent fever, vomiting, hematemesis, or melena.

In the management of sharp and/or pointed FOI, Chevalier Jackson's axiom: "Advancing points puncture, trailing do not"[8] can be helpful to remember. In this, the father of modern endoscopy of the upper airway and esophagus referred to the ability to minimize risk of mucosal injury during retrieval of sharp objects by orienting the object with its sharp point trailing during extraction. Endoscopic retrieval of such objects can be accomplished with a variety of accessories and devices, including a forceps or snare, depending on the particular object and endoscopist experience[6,47,72]. To further provide mucosal as well as airway protection, overtube use is advisable, or alternatively, the endoscope tip can be fitted with a protector hood, as mentioned previously[23,77,81]. Some endoscopists prefer endotracheal

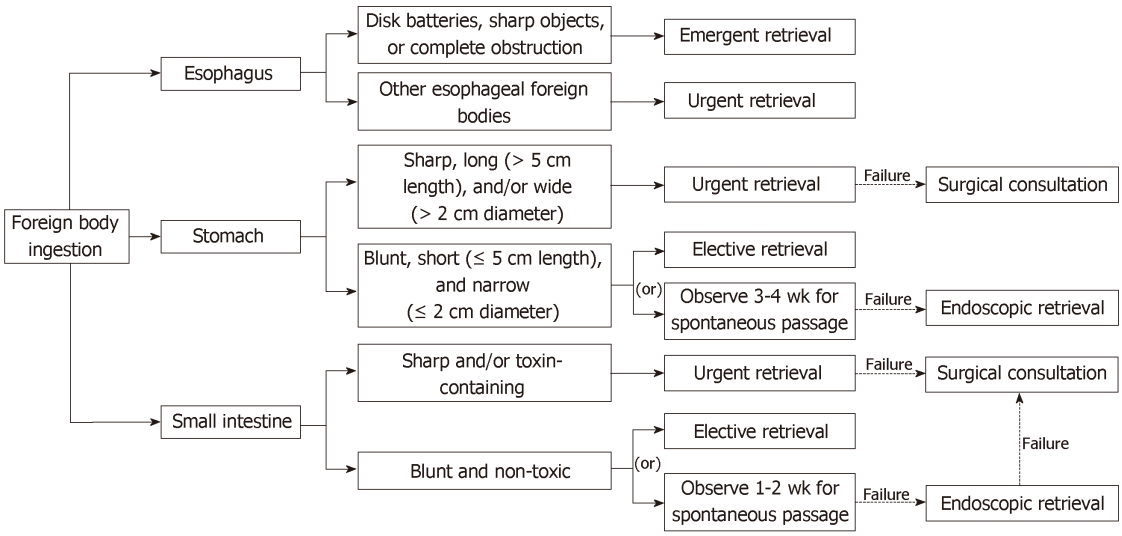

Figure 5 Proposed management algorithm for true foreign body ingestion. Timing (emergent, 2-6 h; urgent, < 24 h) and management of true foreign body ingestions depend on the nature as well as the location of the object. In some instances, imaging and/or surgical consultation may be indicated prior to deciding upon endoscopic intervention; indeed, individualized decisions often need to be made weighing the risks and benefits of endoscopic intervention in a particular case, recognizing that in some scenarios, observation may overall be a safer and more preferable management strategy than endoscopic or other intervention.

intubation for removal of sharp-pointed objects, but this is seldom required from a procedural perspective if an overtube or protector hood is used[47,82].

Long objects

Although typically not sharp, long and/or large (> 5 cm) objects (*e.g.*, toothbrushes, pens, eating utensils, dental appliances) may carry considerable risk of complications when ingested (Figure 7). The majority of such objects are unlikely to spontaneously traverse the duodenal sweep and should thus be removed[3,6,118]. Width/thickness of the object should also be considered in addition to length. The GI tract of younger (pediatric) patients is smaller, thus modified dimension criteria should be applied in these patients.

In general, endoscopic retrieval of long or large objects can be performed after an interval of pre-procedural fasting as long as the patient is asymptomatic. A variety of devices and accessories can be used for endoscopic retrieval; commonly, the object is best grasped with a snare or Roth retrieval net and then maneuvered into an overtube[80] (Figure 8). Once this is achieved, the entire apparatus (*i.e.*, foreign object, overtube, and endoscope) can then be removed from the patient in one motion so as to avoid losing grasp of the object within the overtube[29,119].

Batteries

Due to their small size, slippery texture, as well as increasing prevalence in many everyday electronics (*e.g.*, hearing aids, watches, toys, calculators, *etc.*), disk and button battery ingestion is on the rise, with children under the age of 5 responsible for most cases[6,120,121]. Direct pressure applied to the mucosa by the battery (leading to pressure necrosis), leakage of strongly alkaline contents (causing chemical damage), and generation of an electrical current (due to the production of hydroxide at the negative pole of the battery, resulting in a high pH), contribute to the high risk of liquefactive necrosis and mural perforation that can rapidly occur when a disk battery is lodged in the esophagus[29,122,123]. Lithium battery ingestions are particularly dangerous given their generally larger size and ability to generate more electrical current in a short period of time[124]. Thus, the use of honey (dosed at 10 mL every 10 min) in the prehospital setting, or sucralfate (dosed at 10 mL every 10 min) in the emergency department setting, has been suggested to coat the battery and delay hydroxide generation and exposure[125,126]. In fact, the National Capital Poison Center has recently updated their Battery Ingestion Triage and Treatment Guideline to incorporate the aforementioned suggestions (for up to 12 h after ingestion of a lithium coin battery)[127]. Of note, however, honey should not be given to children under the age of 1 year due to the risk of infantile botulism[128].

Once discovered on imaging, batteries lodged in the esophagus should be emergently removed, as damage to the esophageal mucosa and deeper tissues can occur within hours[129,130]. Endoscopic retrieval using a retrieval net is often successful for this indication[72]. An alternative method is to use a through-the-scope balloon,

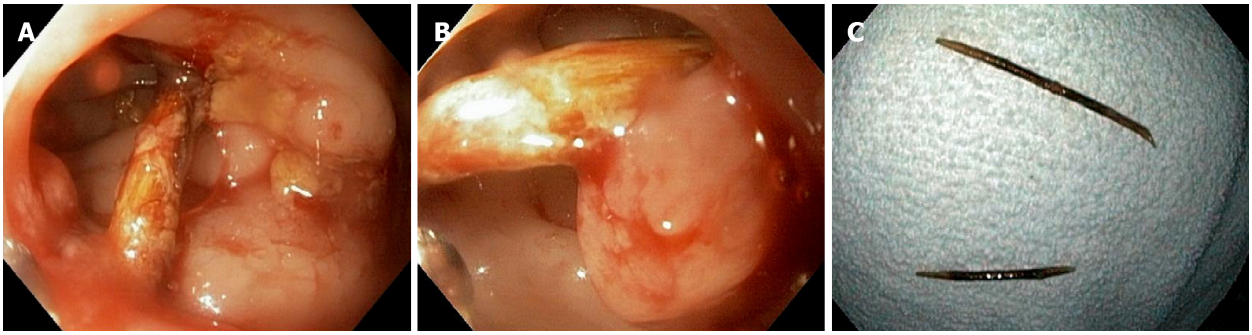

Figure 6 Endoscopic extraction of embedded toothpick. An 82-year-old woman with remote history of accidental toothpick ingestion and presumed spontaneous passage underwent colonoscopy for fecal incontinence. A, B: Upon reaching the rectosigmoid junction, polypoid inflammatory changes were visualized at the base of both ends of what appeared to be an embedded toothpick; C: Colorectal surgery was called to the procedure room, and a multidisciplinary decision was made to attempt endoscopic removal. Using standard biopsy forceps, the toothpick was grasped and, using gentle traction, successfully removed in two pieces.

whereby a balloon is passed through the working channel beyond the foreign body. The balloon is then inflated, and the entire endoscope and balloon are withdrawn, thus pulling the battery up and out of the body[8]. To protect the airway, an overtube or endotracheal tube is necessary with the aforementioned method. In cases where retrieval of the battery from the esophagus is not possible, the foreign body should be advanced into the stomach, grasped or otherwise captured therein, and then removed. The National Capital Poison Center now also recommends endoscopic irrigation of the injured esophagus with 150 mL of 0.25% acetic acid immediately after battery removal (in an attempt to neutralize injury from alkaline batteries)[127,130], but no studies have been performed to evaluate whether this intervention improves outcomes, and the risks may outweigh the benefits in cases where there is no endoscopically visible chemical injury.

Batteries that have spontaneously progressed beyond the esophagus do not necessarily need to be retrieved unless the patient has signs or symptoms of GI tract injury[129]. A large-diameter (> 20 mm) battery remaining in the stomach longer than 48 h, as documented by repeat imaging, however, should be removed (even in the absence of signs or symptoms of injury)[6,131]. Use of emetics and cathartics has been reported, but this practice is not recommended and may be harmful[6,29,131]. Once beyond the duodenum, the majority of batteries, even those that are large and/or long, will be passed out of the body within 72 h[120] unless a pathologic narrowing (*e.g.*, from adhesions) is present. Radiographs can be obtained every 3 to 4 d to ensure progress and ultimate passage[6].

Magnets

Ingestion of magnets can cause severe GI injury and even death. The number of magnets is important, as ingestion of a single magnet is unlikely to result in GI complications, whereas ingestion of more than one magnet may be exceedingly hazardous because of the attractive force generated between magnets, which can lead to fistulization, obstruction, mural necrosis, and perforation[6,80].

Imaging should be considered following magnet ingestion to localize the magnet(s), determine their size, and evaluate for the development of complications. It has been suggested that, when possible, any and all magnets be removed, even if only one magnet is reported or visualized on imaging, as undetected magnets or other ingested metal objects together with a magnet can lead to significant injury[132]. In many instances, however, if a magnet is not large and is already beyond the reach of an upper endoscope or enteroscope, careful monitoring for continued passage through the GI tract is preferable[80,133].

Drug packets

Internal concealment of narcotics or other illicit drugs wrapped in plastic or contained in latex condoms, referred to as "body packing," is a form of drug trafficking[134,135]. Although historically a phenomenon seen only in adults, cases of pediatric body packers (*i.e.*, smuggling "mules") have been reported[80,136,137]. Drug packets can usually be seen by non-invasive imaging modalities (particularly CT)[138,139]. Use of activated charcoal to bind drug and decrease drug absorption or bowel irrigation with polyethylene glycol solution to promote evacuation may be attempted, but data to support these practices are limited. Paraffin or mineral-oil-based laxatives should be avoided due to their ability to degrade latex and thus increase risk of drug exposure[140]. When imaging is equivocal and/or patient history is unreliable,

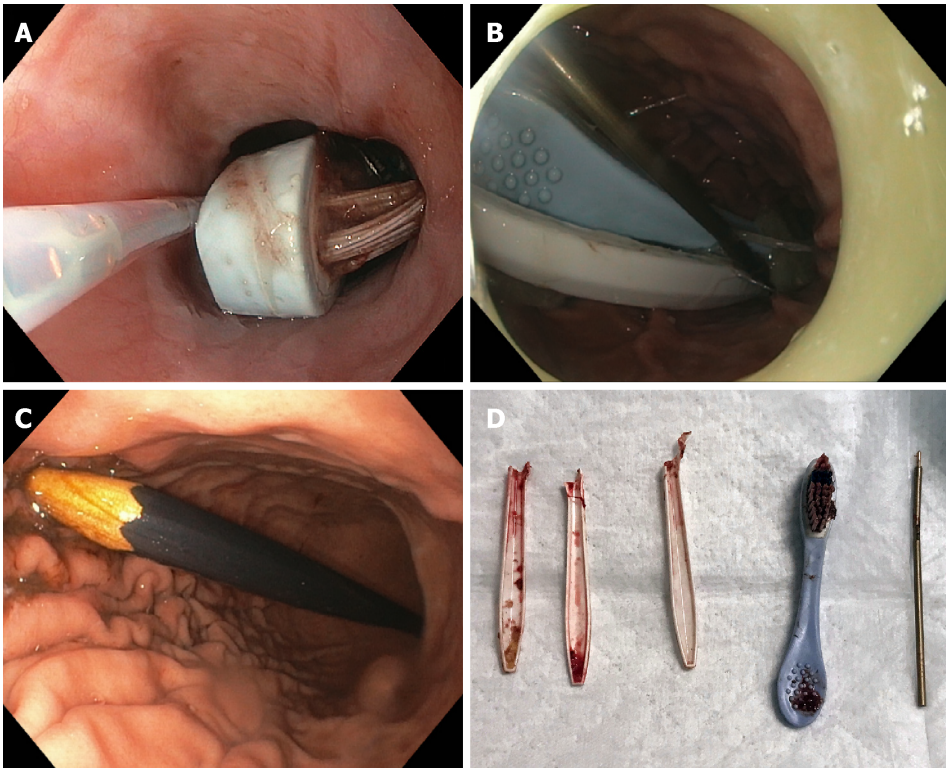

Figure 7 Endoscopic extraction of multiple long objects. A, B: A 36-year-old male was found to have multiple foreign ingested objects in the stomach, including a toothbrush (A), pen cartridge, and several forks (B); C: On subsequent encounters, the same patient was found to have other ingested objects, including pencils; D: Items recovered during endoscopy are shown in.

diagnostic endoscopy can be considered to confirm the presence, location, and number of drug packets. Endoscopic removal, however, should typically not be attempted given the risk of packet rupture, drug leakage, and potentially fatal ensuing events. A Swiss study of 132 patients found the risk of drug packet rupture when left to pass the GI tract on its own to be nil (though the authors acknowledged that variations in risk may exist between different countries based on the quality of the packaging)[141]. Surgical intervention is generally indicated in cases with failure of the packet(s) to progress spontaneously, signs or symptoms of GI obstruction, or suspected packet rupture[47]. On a similar note, endoscopic removal of detergent packets (also known as "laundry pods") is not recommended, as these packets dissolve quickly, and attempted removal can lead to aspiration and other complications[142].

Small intestinal foreign objects

If an object has already passed through the upper GI tract, it will typically continue to pass through the small intestine, into the colon, and out of the body. In some instances, however (*e.g.*, in the setting of jejunal or ileal strictures related to Crohn's disease or radiation), retention may occur in the midgut, *i.e.*, in the small intestine beyond the reach of a standard upper endoscope. In such instances, enteroscopy (*e.g.*, push, balloon-assisted, and laparoscopically assisted) can facilitate access to and removal of retained objects as well as identification of a cause for retention. For example, case reports and series have described the successful use of anterograde and retrograde balloon enteroscopy to retrieve retained video endoscopy capsules (Figure 9)[143-146] as well as other FOIs[147]. Although data on enteroscopy for retrieval of ingested foreign bodies from the midgut are currently limited, accessories such as hoods, baskets, and forceps, do exist for balloon enteroscopes, and thus it represents an option in select cases. In the interim, clinical decision making regarding enteroscopy in the management of FOIs should consider variables such as the nature of the FOI, patient stability, underlying disease and anatomical factors, anterograde vs. retrograde approach, availability of appropriate endoscopic accessories, need for fluoroscopy, and endoscopist expertise[6].

Colorectal foreign objects

Colorectal foreign objects can result from anterograde passage of ingested objects down to the colorectum (Figure 8) or from direct retrograde insertion. Retrograde

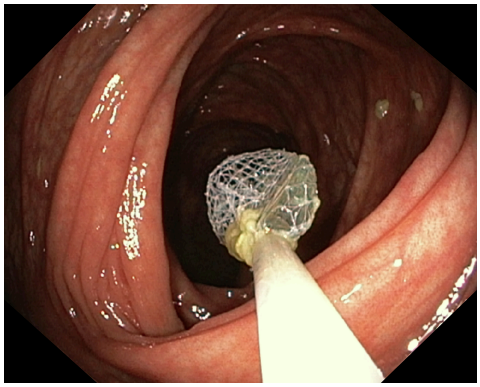

Figure 8 Retrieval of foreign object with Roth retrieval net. A 27-year-old man who reportedly swallowed glass while working under a skylight that shattered. A glass shard was removed from the cecum via colonoscopy with a retrieval net[148].

insertion is usually a result of sexual practices, psychiatric illness, or illicit drug smuggling. Patients with colorectal foreign objects may be asymptomatic or may present with a variety of symptoms, including GI bleeding, tenesmus, large bowel obstruction, peritonitis, or perforation. Blunt objects lying low (distally) in the rectum may be amenable to digital removal under moderate sedation; objects in a more proximal location may require sigmoidoscopic or colonoscopic removal. For sharp and/or pointed objects, a digital rectal exam should be deferred; such objects should be removed under direct visualization, generally with a protector hood or similar apparatus. Large objects (*e.g.*, vibrator or bottle) usually require general anesthesia and anal sphincter dilation or retraction, and some may even necessitate the use of a large-caliber rigid proctoscope (usually performed by a colorectal surgeon). In rare instances, laparotomy may be required.

CONCLUSION

FOI and EFI are common clinical problems which generally require multidisciplinary care coordination. This review has provided evidence- and experience- based guidance and updates regarding the diagnosis and management of FOI and EFI in their various forms and presentations. In many instances, endoscopy is safe and effective and generally the treatment of choice for both FOI and EFI. To further improve patient outcomes associated with these clinical scenarios, well-designed RCTs evaluating pharmacologic, imaging, and endoscopic aspects of the care of patients presenting with FOI and/or EFI may be considered to better formulate evidence-based, cost-effective management strategies.

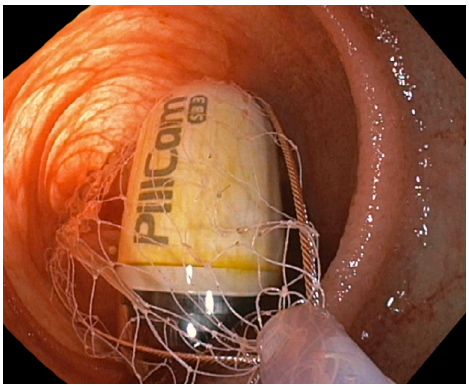

Figure 9 Laparoscopically-assisted enteroscopic foreign object retrieval from the deep small bowel. Retrieval of a retained video capsule in the distal ileum via laparoscopically-assisted anterograde enteroscopy in a patient with Crohn's disease.

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REVIEW

Acute abdominal obstruction: Colon stent or emergency surgery? An evidence-based review

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Abstract

According to the American Cancer Society and Colorectal Cancer Statistics 2017, colorectal cancer (CRC) is one of the most common malignancies in the United States and the second leading cause of cancer death in the world in 2018. Previous studies demonstrated that 8%-29% of patients with primary CRC present malignant colonic obstruction (MCO). In the past, emergency surgery has been the primary treatment for MCO, although morbidity and surgical mortality rates are higher in these settings than in elective procedures. In the 1990s, self-expanding metal stents appeared and was a watershed in the treatment of patients in gastrointestinal surgical emergencies. The studies led to high expectations because the use of stents could prevent surgical intervention, such as colostomy, leading to lower morbidity and mortality, possibly resulting in higher quality of life. This review was designed to provide present evidence of the indication, technique, outcomes, benefits, and risks of these treatments in acute MCO through the analysis of previously published studies and current guidelines.

Key words: Colorectal cancer; Endoscopy; Stent; Surgery; Palliative

Core tip: This review was designed to provide present evidence of the indication, technique, outcomes, benefits, and risks of colon stenting and emergency surgery in

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acute malignant colonic obstruction through the analysis of previously published studies with 1A evidence and current guidelines.

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INTRODUCTION

According to the American Cancer Society[1] and Colorectal Cancer Statistics 2017[2], colorectal cancer (CRC) is one of the most common malignancies in the United States and the second leading cause of cancer death in the world in 2018. Acute abdomen obstructive (AAO) due to CRC occurs in 8%-29% of patients and is a gastrointestinal (GI) emergency requiring urgent decompression considering the risk of necrosis and perforation as a result of massive distension of the loop. Bacterial translocation and imbalance of intracorporal electrolytes also contribute to the high mortality rate[3-5].

In the 1990s, self-expanding metal stents (SEMS) appeared, which were a watershed in the treatment of patients in GI surgical emergencies[6-9]. The initial studies had encouraging results since the use of the stent could remove the patient from a surgical emergency, improve their performance status, reducing not only morbidity but mortality and preventing a colostomy giving them a better quality of life (QOL)[10-13]. Palliative patients were major beneficiaries of this development since they often can not tolerate more invasive surgical procedures, and up to 94% of emergency surgeries can be avoided with this strategy[14].

For patients presenting with acute left-sided colonic obstruction secondary to an operable malignancy, SEMS placement allows colonic decompression, preoperative bowel preparation, and preoperative colonoscopy to assess for synchronous cancers. Patients may then undergo a one-stage surgical procedure, possibly laparoscopically, with a primary anastomosis[6,15].

In the past, emergency surgery (ES) has been the primary treatment for AAO, although morbidity and surgical mortality rates are higher in these settings than in elective procedures[16]. ES in this setting is associated with a morbidity rate of 32%-64%[17] and mortality rate of 15%-34%.

There are currently 13 randomized controlled trials (RCTs)[18-30] and 20 meta-analyses[7,14,15,30-47] reporting results of colonic SEMS as a bridge to surgery. There are also 4 RCTs[12,48-50] and 4 meta-analyses[42,51-53] evaluating SEMS for palliative indications. Nevertheless, there are still doubts about the management of AAO by CRC.

This review was designed to provide present evidence for the indications, techniques, outcomes, benefits and risks of these treatments in the management of acute malignant colonic obstruction (MCO) through the analysis of previously published studies and current guidelines.

SEARCH METHODS

Study selection

A systematic search was performed, with no restriction regarding the idiom or the year of publication, since the inception of database till October 01, 2018 using PubMed, MEDLINE, Web of Science, EMBASE, and Cochran Central Register of Controlled Trials databases. Both MeSH and non-MeSH terms were included in the search.

Eligibility criteria

All studies comparing colonic stent *vs* surgery for acute malignant large bowel obstruction were included. Relevant studies about colonoscopy, acute obstructive abdomen due to neoplasia were also included.

Exclusion criteria

Studies were excluded from this review according to the following criteria: use of the

stent for benign treatment, stents placed by an interventional radiologist; unclear or missing data for the outcomes variables.

Assessment of study quality

Randomized trials (Evidence 1A) were prioritized as well as previous reviews on the topic.

INITIAL CONSIDERATIONS

Bowel obstruction is defined as the absence of gas or bowel movements for ≥ 24 h, and it is associated with abdominal pain, abdominal bloating or distension and the visualization of dilated colon on an abdominal imaging[16,54].

Computed tomography (CT) is recommended when MCO is suspected and[55] can confirm obstruction and clarify the level of the stricture, as well as identify the etiology of obstruction[41,56] .

STENTS INDICATIONS

Indications

Currently, indications for stent placement in patients with MCO are: Stent as a "bridge to surgery" to avoid ES[57]; Palliative CRC patients[58]; Extra colonic tumors causing acute abdominal obstruction (*e.g.*, advanced gastric cancer, ovarian cancer)[59-61].

Contraindications

Signs of systemic toxicity or septic shock as these are signs of colonic ischemia or perforation[62]. Intra-abdominal abscess. Excessively dilated cecum (> 9 cm) as endoscopic insufflation may precipitate colonic perforation. Distal rectal lesions that would require the stent to cross the dentate line as this can induce severe pain, tenesmus, and rectal bleeding[34,63]. Persistent coagulopathy (relative)[64].

Extrinsic obstruction

Rarely, extrinsic lesions can compress the colon causing MCO. The most frequent causes of extrinsic obstruction are primary pelvic malignancies (ovarian, uterine, and bladder cancer), advanced gastric cancer or metastatic lesions to the pelvis[65]. Extrinsic obstruction occurs more frequently in the left colon, especially in the distal region, and in these cases endoscopic tissue biopsy is not technically possible and the exact etiology and extent of obstruction is often not clear[60,61].

Patients with extrinsic colonic obsltruction, in the vast majority of cases, have advanced disease with reduced life expectancy and no potential curative surgical ressection. .Nevertheless, the technical and clinical success of stenting in these cases, is less effective then when apllyied to primary colorrectal tumors, and there no ideal option[59,65].

STENT and chemotherapy

Whether it is in palliative patients or in those who will use the stent as a bridge for elective surgery, there is a high chance of colonic perforation if chemotherapy is associated, especially with angiogenesis inhibitors such as bevacizumab[66,67]. The European Society of Gastrointestinal Endoscopy does not recommend the combination therapy of stent with antiangiogenic drugs[62].

Chemotherapy for metastatic CRC (CRCM) has evolved in the last decade from cytotoxic agents to molecular targeting agents[68]. Currently, four cytotoxic agents [5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin][69,70] and five molecular targeting agents [bevacizumab (BV), cetuximab, panitumumab, aflibercept, and regorafenib] are used as chemotherapeutics for CRCM, given in combination or alone[71-74].

New chemotherapy schedules can take approximately 24 mo[75-77], twelve months longer than that used in the classic 5-FU + leucovorin scheme[78]. Chemotherapy decreases the risk of tumor ingrowth compared to the use of SEMS alone; however, chemotherapy is considered a significant risk factor for long-term complications, including perforation and stent migration[79]. Regarding the use of bevacizumab, studies have reported that it is an independent risk factor for late complications and even without a stent increased the risk of perforation by 19.6 times[80,81].

Considering the benefits of increased survival and QOL achieved by new chemotherapies, there still is a role for stents in palliation, however, with

parsimony[66,82].

TYPES OF COLONIC STENTS

SEMS may be either covered or uncovered; however only uncovered are available in the United States. All colorectal stents work very similarly[83].

The available stents are mostly made of a nickel-titanium metal alloy (nitinol) (Figure 1). An important characteristic of this material is that it is malleable at low temperatures and has strong radial force at body temperature without losing flexibility[84].

Delivery systems can be introduced into the colon parallel to the endoscope, over the wire (OTW) or through the scope (TTS). TTS is typically preferred and facilitates the treatment of right colon lesions[3,85]. Commercially available stents are reported in Table 1.

Covered vs uncovered stents

Covered stents are mainly used in the establishment of colonvesical fistulas, coloenteric and cervicovaginal malignancies[86]. Although the theoretical advantage of covered stents is that they have a lower risk of tumor ingrowth, they are also more likely to migrate compared to uncovered stents.

In a randomized trial[84] including 151 patients with AAO by CRC, there was no difference in the clinical success rate for the placement of covered stents compared with uncovered stents (96% *vs* 92%). There was a higher rate of migration (21% *vs* 2%) and a trend towards less tumor ingrowth in covered stents (4% *vs* 15%). There were no differences in relation to adverse events or obstruction by debris.

ADDITIONAL DIAGNOSTICS AND EXAMS

The diagnosis of colonic obstruction is made through symptoms and complemented by imaging tests (for example, simple radiography and/or CT (Figures 2 and 3). Additional exams such as colonoscopy may be performed prior to stent placement procedure. Pre-procedure colonoscopy may provide direct endoscopic visualization of the site of obstruction, and tissue biopsies can be performed for histological diagnosis if needed. Important tumors characteristics can also be ascertained , such as precise location, length of stenosis, topography (extrinsic or intrinsic), and adjacent anatomic considerations (angulation, mucosa inflammation, ischemia or diverticulae)[87,88].

The degree of obstruction should be assessed by attempting to navigate the stenosis with the endoscope; however, it is not necessary to advance the endoscope through the tumor to perform stent placement. Examination with a water-soluble enema or rectal CT may be useful, but not absolutely necessary, to obtain a map of the colonic anatomy, length of stenosis, and degree of obstruction. This radiographic evaluation may also identify additional sites of obstruction that may prevent successful stent placement[33,56].

PROCEDURE

Preparation of colon

Although patients may have AAO, bowel preparation should be attempted and preparation depends on location and degree of obstruction: For partial obstruction in the distal colon, two water-soluble enemas (250-500 mL) are sufficient; For partial obstruction of a proximal lesion, oral colon preparation may be attempted and discontinued if symptoms such as abdominal pain or emesis occur[89]; For complete colonic obstruction, oral preparations are contraindicated due to high risk of perforation. Rectal water-soluble enemas should be considered[90].

Use of pre-procedure antibiotics

Prophylaxis is not mandatory for patients undergoing stenting. However, in patients with complete obstruction, we suggest prophylaxis considering the risk of micro perforation and bacteremia during insufflation[62,91].

Sedation

Lower endoscopic procedures can typically be performed anywhere on the sedation spectrum, from sedation to general anesthesia. However, this is not applied to

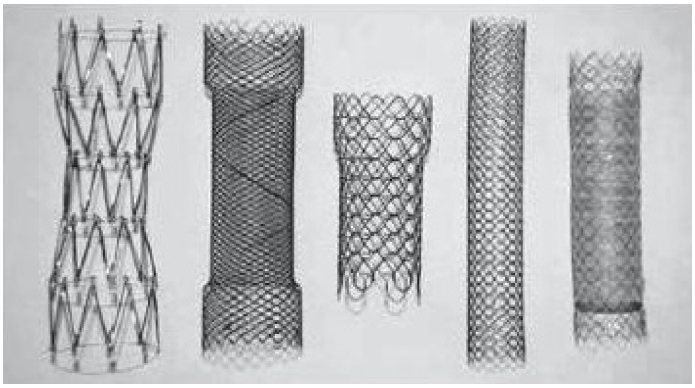

Figure 1 Stent models, left to right: Colonic Z (Cook), Evolution colonic (Cook), Wallflex (Boston), D-type colonic not covered (Taewoog), type colonic covered (Taewoong). All FDA approved stents.

patients who need to use a stent because they are in an obstructive emergency. General anesthesia with active airway management should be mainly performed to prevent bronchoaspiration with feculent emesis for example and also does not move at the time of the procedure increasing the chance of perforation[92,93].

Procedure

Stents are always placed under endoscopic guidance with the aid of fluoroscopy[62,94] (Figure 4). During colonoscopy, limited insufflation should be used to minimize the risk of perforation due to the risk of a closed loop between the obstructive lesion and the ileocecal valve. The use of carbon dioxide has largely supplanted air for this procedure, and most complex therapeutic cases[95]. A water-immersed colonoscopy is another technique that can be used to minimize bowel distention[96].

Upon reaching the lesion, an attempt can be made to cross the stenosis with the endoscope. However, if the endoscope does not traverse through the obstruction easily, a 0.035-inch guidewire may be passed through stenosis under fluoroscopic guidance.

The first RCT[48] comparing stenting versus ES in palliative patients included balloon dilation of the stenosis prior to stent placement, which is no longer considered and acceptable practice. If endoscope passage through the stenosis is not possible, fluoroscopic guidance is preferred to balloon dilation as the latter is associated with increased risk of perforation[84].

After confirming the length of stenosis, either through the passage of the endoscope or with contrast injection under fluoroscopic guidance, technique of stent placement depends on the type of stent being used.

STENT PLACEMENT

TTS

For this method, a therapeutic endoscope is needed to introduce the stent through the working channel (Figure 5). If the stenosis cannot be traversed, contrast injection helps to delineate the stenosis and to confirm guidewire placement trough the stenosis under fluoroscopy.

The stent is then passed over the guidewire to the proximal margin of the tumor and then implanted under fluoroscopic guidance and endoscopic visualization of the distal portion of the stent. Each end of the stent must be at least 2 cm longer than the stenosis (4 cm of safety margin), as these stents typically shorten after deployment and expansion[62,85,97] (Figure 6).

To prevent migration, it is not recommended that the endoscope be passed through the stent once the stent is placed, although endoscopic/fluoroscopic visualization should be used to rule out early complications.

OTW

After the guidewire placement, endoscopic visualization is still preferred, however, not absolutely essential[64]. This technique may be helpful when there is an acute angulation or others factors limiting endoscopic visualization. The stent is inserted over the guidewire and implanted under fluoroscopic guidance (Figure 7).

The correct position of the stent reveals a waist in the center of the stent that crosses the tumor with a widening of the proximal and distal ends. If either end of the stent is

Table 1 Commercially available colorectal stents

Manufacturer and model	Material	Delivery system	Diameter (mm)	Flare	Flare diameter (mm)	Length (mm)	Covered/uncovered
Boston Scientific							
Wallstent Colonic[1]	Nitinol	TTS	22, 25	1	27, 30	60, 90, 120	Uncovered
Wallstent Endoprothesis[1]	Stainless steel	TTS	20, 22	0	–	60, 90, 120	Uncovered
Ultraflex Precision Colonic[1]	Nitinol	OTW	25	1	30	57, 87, 117	Uncovered
Micro-Tech Europe		OTW	30	0	–	75, 88, 112, 123, 136	Uncovered/fully covered
Micro-Tech Europe Colon and Rectum stent	Nitinol	OTW	20, 30	2	26, 36	60, 80, 100	Uncovered/partially covered
Leufen Medical GmbH		TTS	25	2	30	80, 100, 120	Uncovered
Colon Rectum Stent	Nitinol	OTW	25, 30	2	30, 36	80, 100	Uncovered/partially covered
		TTS	25	2	30	80, 100	Uncovered
Cook							
Evolution Colonic[1]	Nitinol	TTS	25	2	30	60, 80,100	Uncovered
MI Tech							
Hanarostent Colon/Rectum[1]	Nitinol	TTS	22, 24	2	26, 28	80, 110, 140, 170	Uncovered
		TTS/OTW	20, 24	2	26, 32	60, 90, 100, 120, 130, 160	Fully covered
		OTW	24	2	32	50,80,110,150	Fully Covered
Choostent Colon/Rectum	Nitinol	OTW	22,24	2	30, 32	100, 180	Fully covered
EndoChoice		OTW	22,24	2	30, 32	80, 120	Fully covered
Bonastent	Nitinol	TTS	22, 24, 26	0	–	60, 80, 100	Uncovered/partially covered
Taewoong Medical							
Niti-S Enteral Colonic D-type[1]	Nitinol	TTS	18, 20, 22, 24, 26, 28	0	–	60, 80, 100, 120	Uncovered
Niti-S Enteral Colonic S-type[1]	Nitinol	TTS	20, 22	2	28, 30	60, 80, 100, 120	Fully/partially covered
		OTW	22, 24, 26, 28	2	30, 32, 34	60, 80, 100, 120	Fully/partially covered
Self expandable Stent							
Braile Endomédica	Nitinol	TTS	26	0	-	70, 100, 130	Partially covered

[1]FDA approved. TTS: Through the scope; OTW: Over the wire.

not adequately expanded to produce a waist, it may be too short to cross the stenosis. In such cases, a second or third overlapping stent can be used without removing the first to completely cross the stenosis[98].

POST-PROCEDURE CARE

After stent placement in the left colon, stool softeners should be used to prevent fecal impaction within the stent[62]. Low-residue diets added to the use of polyethylene glycol should be followed. Laxative dose titration may be required. Patients should be instructed to avoid high-fiber foods, such as many fruits, vegetables, and whole grains[98]. Patients with stents in the transverse or right colon may resume normal diets, as the feces in these locations is typically liquid[98].

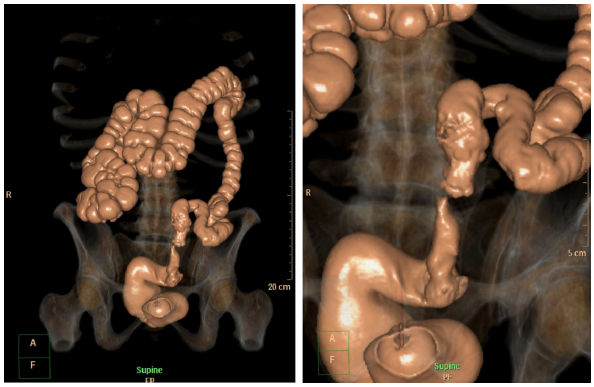

Figure 2 Virtual Colonoscopy showing a malignant stricture in the distal left colon.

ADVERSE EVENTS

Colonic SEMS placement seems to be relatively safe and effective and has some advantages over surgery, but is associated with an overall complication rate of up to 25%[99-101]. Clinical and technical failures are greater in strictures longer than 4 cm and more adverse events, especially perforation, are reported in complete obstruction[80].

Adverse events may be categorized into minor and major or early (≤ 30 d) and late (> 30 d). Example of major adverse events includes intestinal perforation, obstruction requiring new procedures, bleeding, migration, aspiration during sedation, and death. Typical minor adverse events includes abdominal pain, colic and tenesmus[3].

Perforation

This may occur late or immediately after the procedure and is associated with poor outcomes[9]. Several factors can increase the risk of perforation including radiotherapy and chemotherapy as well as colonic anatomy[3,66,67]. A meta-analysis in 2018, including palliative patients revealed a perforation rate of 9.5%[53].

Stent migration

Occurs in approximately 10% when used as a bridge to surgery and in 1% of palliative patients, usually one week after insertion. The main causes of migration include incorrect stent selection, stent dimensions being too narrow, small, or short, mild stenosis that is not obstructive, and improvement of stenosis due to radiotherapy or chemotherapy[7,32,53]. Other less common factors that may precipitate stent migration include extrinsic lesion, dilation of stenosis, or use of covered stents.

Stent obstruction

Occurs in approximately 11.1% of palliative patients. This occurs due to tumor overgrowth at the proximal or distal margins of the stent or through tumor in growth through the cells of the stent[53]. Possible endoscopic treatments for stent obstruction include laser ablation of the tumor, argon plasma coagulation or placement of new stent[48,102].

Hemorrhages

Immediate post-procedure bleeding may occur due to irritation of the colon mucosa by stent flanges, tumor friability, trauma due to either stent passage or guidewire placement, or endoscope trauma. Late bleeding may be due to stent related ulcerations or erosions in the colonic mucosa[64].

Pain

Mild abdominal pain is common and may be prolonged up to five days after stenting. For this, the use of simple analgesics can be helpful. Opioid analgesics may be required within 48 to 72 h of stenting due to expansion of the stent with consequent worsening of pain[34,85]. For low rectal lesions, stent-induced irritation of the nerve endings near the squamous-columnar junction should be avoided.

Colonic decompression failure

Despite the high technical success of stent implantation, failure of colonic decompression can occur. This often results in urgent surgery and is considered a serious adverse event[9,103]. The most common reasons are described below[91]: Other additional sites of intestinal obstruction; Stent shorter than stenosis length; Incomplete stent expansion; Stent migration; Underlying motility disorder; Fecal impaction.

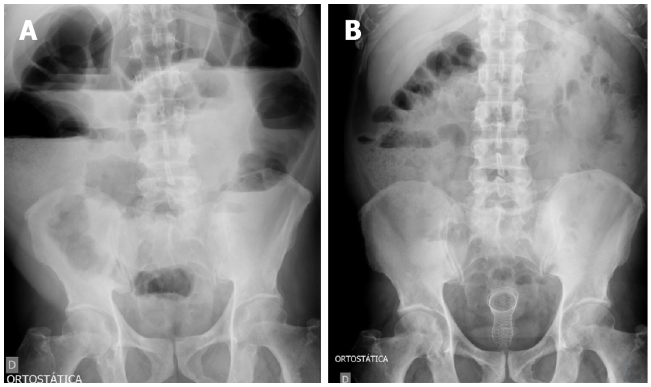

Figure 3 Radiography images. A: Radiography showing signs of a distal obstruction; B: Radiography of the same patient showing improvement after stenting and decompression. **Figure 4** Stents procedure. A: Guide-wire placement through the stricture after contrast study; B: Stent deploying through the scope; C: Stent placement showing the stricture in the middle of the stent; D: Final stent position.

EVIDENCE 1A IN LITERATURE

In a recent systematic review and meta-analysis performed by Arezzo *et al*[15], used only RCTs with a total of eight articles: Mortality rate of 9.9% in ES group and 9,6% was demonstrated in the SEMS group; Adverse events rate of 51.2% was demonstrated in the ES group versus 33.9% in the patients with stent; Temporary colostomy rate of 33.9% was demonstrated in the stent group *vs* 51.4% of patients undergoing ES; The definitive colostomy rate of 22.2% was demonstrated in the stent group versus 35.2% demonstrated in patients of ES group; Regarding the success of the primary anastomosis, there was a 70% rate for the stent group versus 54.1% for the ES group; The need for surgical intervention due to adverse events was 10.9% in the patient with SEMS versus 8.7% in the ES group; The operating time: 172 min in patients submitted ES and 146 minutes in the SEMS group; The hospitalization time was, on average, 14.5 d for patients submitted to ES and 15.5 d for those submitted to STENT; Tumor recurrence was 40.5% in patients in the stent group and 26.6% in the ES group (Table 2).

Stent in palliative patients

A recent systematic review and meta-analysis performed by Ribeiro *et al*[53] in 2018, compared the use of stents to surgical intervention, only in palliative patients, as a definitive treatment. Only RCTs were included, with a total of four articles including 125 patients: 30-d mortality rate of 6.4% in patients submitted ES *vs* 6.3% in the stent group; Analyzed survival was 244 d in the ES group and 279 d in the SEMS group; Clinical success was 84% in the SEMS group and 96% in the ES group; 30-d adverse event rates were 36.5% in the stent group and 24% in the ES group; Technical success was favorable to the surgery group (84% for stent group and 97% for ES group); Rate of permanent colostomy was higher in the surgery group (86.1% versus 14.3%); Length of intensive care stay was not statistically significant between groups; The mean time of hospitalization was 35.5 d for patients undergoing ES and 17.5 for the stent group; Perforation was the most common complication found in the stent group, representing 42.8% of total adverse events, with six of sixty-three patients (9.5%) having perforation, one (1.5%) migration and seven (11.1%) obstruction.

CONCLUSION

Studies comparing emergent surgery to the use of stents as a bridge to surgery demonstrate a lower rate of a temporary and permanent stoma and a lower short-term morbidity, in a patient undergoing stent placement. This may also positively influence patient's QOL, however, questions remain regarding longer-term durability. Until more long-term oncological studies are available, stenting cannot be established as the gold standard of treatment. Regarding the use of stents in acute abdominal obstruction in palliative patients, mean survival, early complications, ICU length of stay, and mortality are similar to surgery. Surgery was associated with greater clinical success, while stents demonstrated shorter hospital stay and fewer definitive stomas. Therefore, stenting may be an alternative for patients with incurable obstructive tumors in acute abdomen, with the advantage of early hospital discharge and the

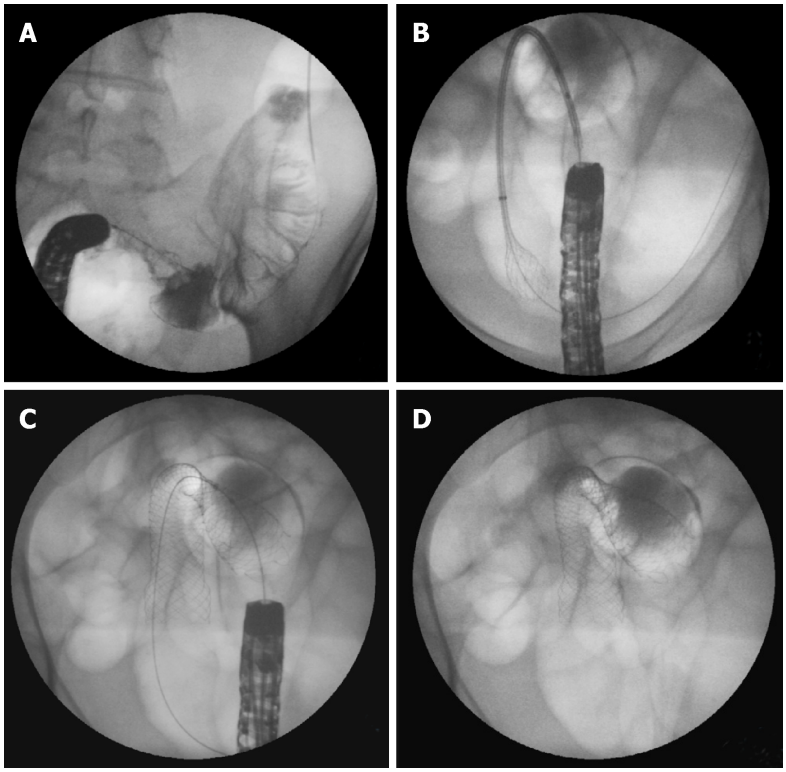

Figure 4 Stents procedure. A: Guide-wire placement through the stricture after contrast study; B: Stent deploying through the scope; C: Stent placement showing the stricture in the middle of the stent; D: Final stent position.

potential for improved QOL with avoidance of a permanent stoma.

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Table 2 Outcomes in studies with evidence 1A (Metanalyses of randomized studies)

Outcome	Stent as bridge to surgery;Arezzo *et al*[13], 2017	Stent as bridge to surgery;Arezzo *et al*[13], 2017	Palliative patients;Ribeiro *et al*[51], 2018	Palliative patients;Ribeiro *et al*[51], 2018
	Stent	Emergency surgery	Stent	Emergency surgery
No. of patients	251	246	63	62
Mortality	9.6%	9.9%	6.3%	6.4%
Adverse events	33.9%	51.2%	36.5%	24.1%
Survival	NA	NA	279 d	244 d
Clinical success	NA	NA	84%	96%
Technical success	NA	NA	84%	96%
Temporary colostomy	33.9%	51.4%	NA	NA
Definitive colostomy	22.2%	35.2%	14.3%	86.1%
Primary anastomosis	70%	54.1%	NA	NA
Hospital stay	15.5 d	14.5 d	17.5 d	35.5 d
ICU hospitalization	NA	NA	0	1 d

NA: Not available; ICU: Intensive care unit.

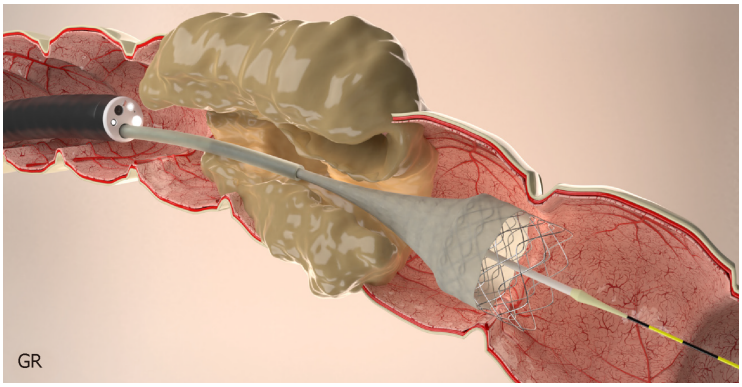

Figure 5 Stent placement by Through the scope technique.

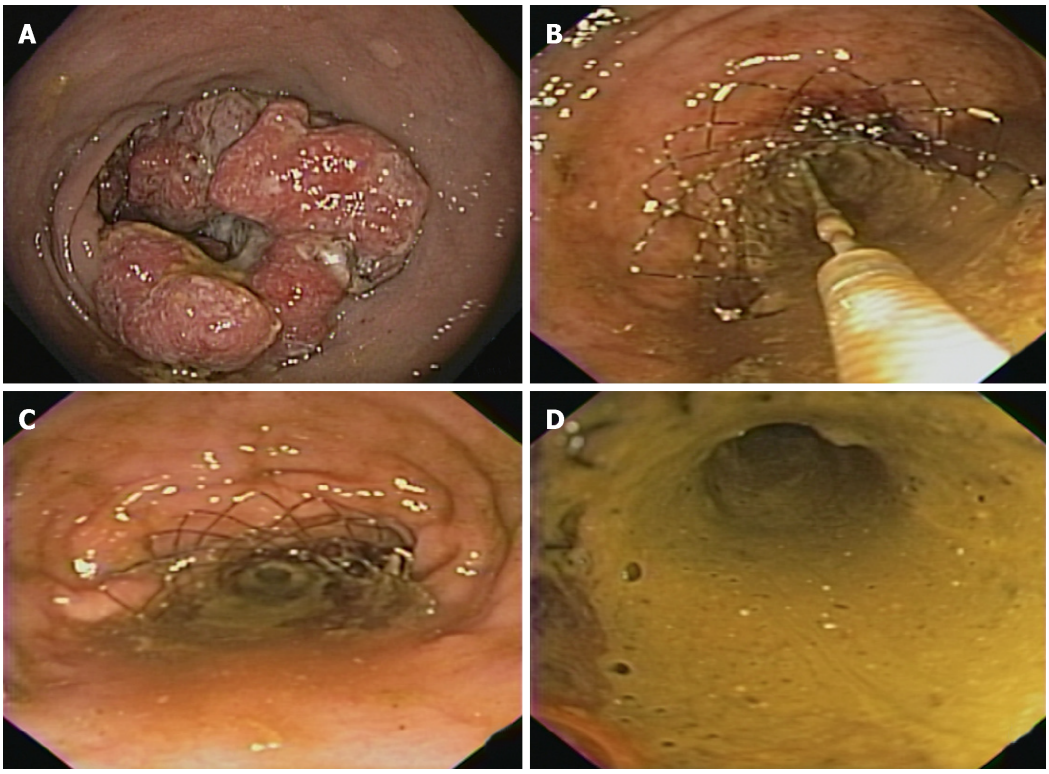

Figure 6 The stent is passed over the guidewire to the proximal margin of the tumor and then implanted under fluoroscopic guidance and endoscopic visualization of the distal portion of the stent. A: Malignant lesion causing colonic stenosis; B: Stent deployment; C: Stent immediately after deployment; D: Fecal contents coming through the stent after decompression.

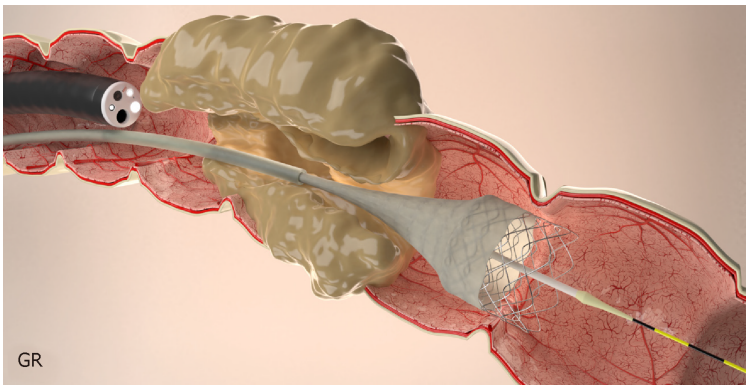

Figure 7 Stent placement by Over-the-wire technique.

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MINIREVIEWS

Simulation in endoscopy: Practical educational strategies to improve learning

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Abstract

In gastrointestinal endoscopy, simulation-based training can help endoscopists acquire new skills and accelerate the learning curve. Simulation creates an ideal environment for trainees, where they can practice specific skills, perform cases at their own pace, and make mistakes with no risk to patients. Educators also benefit from the use of simulators, as they can structure training according to learner needs and focus solely on the trainee. Not all simulation-based training, however, is effective. To maximize benefits from this instructional modality, educators must be conscious of learners' needs, the potential benefits of training, and associated costs. Simulation should be integrated into training in a manner that is grounded in educational theory and empirical data. In this review, we focus on four best practices in simulation-based education: deliberate practice with mastery learning, feedback and debriefing, contextual learning, and

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innovative educational strategies. For each topic, we provide definitions, supporting evidence, and practical tips for implementation.

Key words: Simulation; Endoscopy; Gastrointestinal; Education

Core tip: In gastrointestinal endoscopy, simulation-based training has been shown to improve learning outcomes and performance in the clinical setting and offers unique advantages to trainees and educators. Four best practices, which are grounded in evidence and can help maximize the learning benefits of simulation-based training, are deliberate practice with mastery learning, feedback and debriefing, contextual learning, and innovative educational strategies.

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INTRODUCTION

Simulation-based training allows learners to acquire knowledge, skills and behaviors in a low-risk environment[1]. In gastrointestinal endoscopy, current evidence supports the use of simulation-based training for novice endoscopists to promote skill acquisition, improve performance of initial clinical procedures, and accelerate the learning curve[2-6]. Additionally, simulation can be used to enhance endoscopic non-technical skills and train advanced endoscopic procedures, such as polypectomy[7-9]. Simulation offers an ideal environment for training, as individuals can engage in sustained deliberate practice, work through tasks at their own pace, and build a basic framework of skills and techniques. Importantly, trainees can make mistakes with no patient risk and learn from those mistakes[10]. Simulation also offers advantages for educators, as they can systematically vary training tasks to enhance learning and focus solely on the learner rather than juggle teaching and clinical roles[11].

Despite these advantages, simulation-based training is not universally effective. For example, a 2004 study showed that simulation has no effect on endoscopic skill-acquisition when delivered without feedback from instructors[12]. Simulation is an educational platform through which endoscopy training can be delivered to achieve specific, pre-defined learning goals[13]. Simply providing trainees with access to simulators does not guarantee learning. To be effective, simulation must be integrated into training in a thoughtful and purposeful manner. Additionally, the rationale for incorporating simulation into curricula depends on the magnitude of training benefits, potential cost savings from accelerated learning, and training needs[14]. Overall, the integration of simulation-based training should be thoughtful, deliberate, and grounded in evidence to maximize its learning benefits and outweigh associated costs[15].

This review focuses on four best practices in simulation-based education which can be used to enhance endoscopic training using simulators: (1) deliberate practice with mastery learning; (2) feedback and debriefing; (3) contextual learning; and (4) innovative educational strategies. Within these topics, we will discuss the empirical data supporting their use and practical tips for implementation (Table 1). The benefits of simulation-based training in endoscopy and details of specific endoscopic simulators and curricula have been summarized in multiple recent systematic reviews, and will not be reviewed in depth[2-6]. Additionally, as there is a lack of data on costs associated with endoscopic simulation, this topic will not be covered in this review[16].

DELIBERATE PRACTICE WITH MASTERY LEARNING

Not all practice is perfect. Practice must be purposeful and systematic or "deliberate".

Table 1 Best practices in endoscopic simulation-based training

Educational Strategy	Key points
Deliberate practice with mastery learning	Deliberate practice: repetitive performance of a skill, constructive feedback, and exercises to correct errors and improve performance
	Mastery learning: consistently demonstrating a predefined level of proficiency in a task. Key principles include: baseline assessment; clear and progressive learning objectives; minimum passing standards; educational activities based on predefined objectives and standards; and serial formative assessments to gauge progress
Feedback and debriefing	Endoscopic simulation in the absence of feedback may be ineffective
	Feedback should be simple, goal-directed, based on observable behaviors, and ideally delivered during a debrief at the end of a simulated procedure
	Educators may supplement feedback with validated endoscopic assessment tools and input from other sources, such as nurses, anesthesiologists, and standardized patients
	Debriefing should be a two-way process through which trainees and their trainers identify gaps in performance, explore the basis of those gaps, and establish tasks to improve performance
Contextual learning	Initial training should focus on acquisition of basic skills such as endoscope navigation and torque steering, and progress to simulated tasks of increasing complexity and difficulty
	The introduction of team-based practice through hybrid simulation models can allow trainees to practice non-technical skills, such as communication, decision making, leadership, and crisis management
	Varying tasks during training can better prepare trainees to handle variation in anatomy, pathology, and difficulty during real procedures
Innovative educational design	Endoscopy simulation curricula grounded in educational theory and empirical data have been shown to improve transfer of learning outcomes to the clinical environment
	Training programs can improve learning by implementing simulation sessions at more widely spaced intervals
	Just-in-time simulation training may be used to allow trainees to "warm-up" before performing complex tasks in the clinical environment
	Novel educational strategies emerging in simulation include the application of game design elements and the use of head-mounted displays to create an immersive experience

Deliberate practice involves focused repetitive performance of a skill, coupled with constructive feedback that identifies weaknesses, and promotes self-reflection and error correction to improve performance[17]. Simulation-based training should be delivered in such a way that it allows learners to practice important skills, receive focused feedback, and improve until they achieve mastery. Mastery refers to the ability to consistently demonstrate a predefined level of proficiency on a task before advancing to the next task[18,19]. In this way, individuals progress through tasks of increasing level of difficulty. Key principles in mastery-learning models include a baseline assessment to determine the appropriate level of difficulty of initial simulation-based activities, clear and progressive learning objectives, minimum passing standards (*i.e.*, learning outcomes), educational activities focused on achieving predefined objectives and standards, and serial formative assessments to gauge progress[19,20]. For mastery learning to be most effective there should be multiple different simulation experiences which increase in challenge.

In a recent systematic review of studies in procedural settings, such as surgery and airway management, simulation-based training with mastery learning was associated with better learning outcomes as compared to training without[18]. Additionally, randomized trials in resuscitation and laparoscopic surgery have shown that deliberate practice-based models lead to superior performance in both the clinical and simulated settings[21-24]. In endoscopy, no studies exist which directly compare mastery learning or deliberate practice with other simulation-based learning strategies. One study, however, found that a mastery learning-based simulation curriculum, as compared with no training, resulted in superior clinical colonoscopy performance[25]. Two other pre-post studies found that mastery learning-based curricula resulted in improved performance of simulated colonoscopy[26,27].

Simulation offers an ideal setting for trainees to engage in mastery learning principles and deliberate practice without posing risk to patients[28]. The simulated environment allows learners to repetitively perform the intended skills, receive

focused feedback to identify and correct errors, and adjust training to target specific skills or build upon existing competencies with increasing levels of challenge[17]. Despite these potential advantages, incorporating mastery learning principles poses several challenges. First, as trainees are required to all meet the same objectives, training time will vary. In many cases, a mastery model will require more time[18]. Additionally, learning objectives, key simulation-based metrics and minimum passing standards in endoscopy are not well defined.

FEEDBACK AND DEBRIEFING

Provision of data on a performance (feedback) and conversations about the performance (debriefing) drive improvement and are essential components of simulation-based training[29,30]. Endoscopic simulation in the absence of these elements may be ineffective[2,12]. Additionally, a recent randomized trial demonstrated that a structured, simulation-based curriculum which included feedback and debriefing with expert endoscopists, led to superior transfer of skills to the clinical environment, compared to self-regulated simulation-based training with no feedback or debriefing[31]. Given the importance of these practices, it is important to align feedback and debriefing with the goals of endoscopic training. Practical considerations include the timing of feedback, the content, and the manner in which feedback is delivered.

In the simulated setting, trainees can progress through cases and solve problems independently with no risk to patients. This allows learners to receive feedback after completion of a procedure, a practice that is more effective for endoscopic skill-acquisition compared to feedback received during a procedure[32]. Constant feedback may place an increase cognitive load on novice endoscopists as they attempt to focus on both the procedure and their instructors' feedback[33]. Additionally, trainees may begin to rely on feedback as instruction to guide them through procedures and the skills is not optimally learned[34]. Feedback during a procedure should be limited to providing key information when required. Additionally, when receiving feedback during a procedure, the trainee should be asked to briefly stop what they are doing so they can focus on the feedback and then proceed with the procedure. Delivery of feedback during a post-procedure debriefing session is key as it allows the trainee and trainer to mutually identify gaps in training, explore the basis of the gaps, and set activities for skills improvement[35].

In keeping with the principles of mastery learning and deliberate practice, feedback should be specific, goal-directed, actionable, and focused on improvement[17,36,37]. Feedback should be non-judgmental, relate to pre-specified objectives, it should be based on observable behaviors and it should focus on well-defined and achievable points to avoid overburdening the trainee. Engaging trainees in a two-way feedback conversation is crucial, as it helps to promote self-reflection. Feedback should aim to foster trainee's conscious understanding of the procedure. As trainees advance, the feedback conversation should focus on critical challenges that arose during the simulated procedure, encourage the learner to reflect on the problem and propose potential solutions which can be then be discussed[11]. Questioning encourages active engagement, reflection and independent thought rather than simply being informed of the best option[37].

Trainers can supplement feedback discussions with objective indicators of performance such as a video of the simulated procedure or data from endoscopy assessment tools with strong validity evidence. These tools, which include the Gastrointestinal Endoscopy Competency Assessment Tool (GiECAT)[38], the Mayo Colonoscopy Skills Assessment Tool (MCSAT)[39], the Assessment of Competency in Endoscopy (ACE) tool[40], and the Joint Advisory Committee of GI Endoscopy's Direct Observation of Procedure (JAG DOPS) Assessment Tool[41], can help guide debrief sessions and identify areas of weakness. Feedback from other sources can add another dimension to simulation-based training sessions and help to further characterize trainees' deficiencies. For example, the Nurse-Assessed Patient Comfort Score (NAPCOMS) may be employed with high-fidelity simulators where indicators of patient comfort and sedation are available throughout the procedure[42]. Additionally, training programs can implement a hybrid simulation model, in which trainees practice on a simulator while interacting with a standardized patient (actor portraying a patient)[43]. Through these simulated cases, standardized patients and nurses can participate in debriefing and act as additional sources of feedback. They can also provide insight into the integrative and cognitive aspects of endoscopy, in addition to the technical aspects. Proficiency in all three of these domains is required for competence in endoscopy, and thus they are increasingly incorporated into simulation-based curricula in endoscopy and assessment tools[31,44].

With a growing emphasis on patient safety and a shift towards competency-based postgraduate training curricula in gastroenterology, the provision of feedback and debriefing to enhance performance is crucial[45,46]. Using the large body of empirical research on these topics, instructors can help trainees continually build upon their competencies in endoscopy.

CONTEXTUAL LEARNING

A fundamental concept for instructional design of endoscopic simulation-based training curricula is the applicability, or transfer of training experiences to clinical performance. This transfer can be affected by a range of factors related to the context of training, including trainees' developmental levels, provision of team training, and task variability[30].

Simulation-based training should match specific learning objectives and a learner's developmental level. For example, novice endoscopists can acquire the basic skills of video interpretation, endoscopic handling, and torque steering by practicing on a low-fidelity, bench-top simulator[47]. Training on low-fidelity simulators allows educators to attach precise tasks with physical platforms to target specific learning objectives, a concept known as functional task alignment[13]. This design approach has been identified as a key feature of effective simulation in multiple systematic reviews[1,20,48]. In a recent randomized trial, learners progressed from a low-fidelity, bench-top simulator to a virtual reality simulator with higher fidelity and completed simulated cases in order of increasing complexity and difficulty (Figure 1)[47]. This progressive model of learning improved skill acquisition and transfer of skills to the clinical setting compared to a curriculum using only high-fidelity simulation, supporting the notion that aligning task difficulty to learner skill allows learners to be optimally challenged, which, ultimately, enhances learning[49].

Simulation also offers opportunities to train endoscopists in team-based settings using the aforementioned hybrid simulation model[8,43]. In this model, simulators are linked to a simulated patient and other team members, such as an endoscopy nurse or anesthesiologist. Learners can engage in these simulations in the naturalistic setting of an endoscopy suite and perform procedures while building their skills in communication, decision making, leadership, coordination, and crisis management. Practicing in team-based settings can help automate such behaviors, making them more resilient to the effects of stress, which, in turn, leads to improved performance under stressful conditions[50]. Recent randomized trials support the use of hybrid simulation in endoscopy as a means to improve transfer of critical non-technical skills to the clinical environment[7,31,47].

Another important factor in the applicability of training experiences to the clinical environment is task variability. Live endoscopic procedures present variation with respect to anatomy, procedural difficulty, and pathology encountered. Varying tasks during simulation-based training can increase exposure to a broader range of endoscopic skills and situations, and result in enhanced initial skill acquisition and long-term retention of skills[1,51]. While no studies have examined the impact of task variability in endoscopy, a study from the laparoscopic surgery literature suggests that simulation-based training incorporating variability improves flexibility of trained skills among trainees. Endoscopy teachers can incorporate these principles by using a combination of different cases on both low- and high-fidelity simulators, as described above, and incorporating modules to train specific technical skills, such as polypectomy, or cognitive skills, such as lesion recognition[9].

INNOVATIVE EDUCATIONAL DESIGN

Endoscopy curricula are increasingly incorporating instructional design elements grounded in educational theory and empirical findings from the educational literature. Recent studies by Grover *et al*[7,31,47] have demonstrated the potential benefits of this strategy, with trials of simulation-based training with a structured curriculum, a progressive learning model, and with structured non-technical skills training resulting in improved transfer of skills to the clinical environment. Additionally, there are several emerging educational strategies that can potentially be applied to endoscopic simulation-based training including spaced practice, just-in-time training, gamification, and immersive virtual reality.

In spaced practice, training is separated into several discrete sessions over a prolonged period. In contrast, most endoscopy curricula are delivered as massed practice, with training taking place during a single time period lasting hours or days[2].

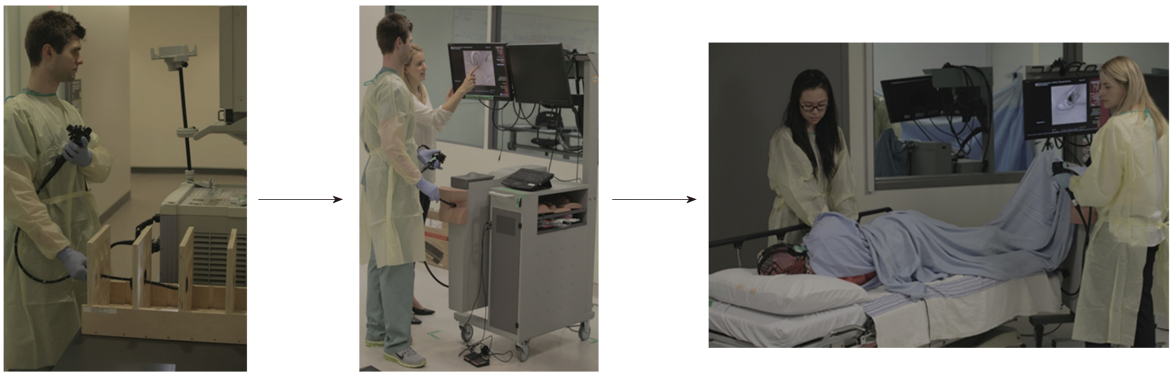

Figure 1 An example of a progressive model of endoscopic simulation-based training whereby learners complete tasks of progressively increasing difficulty as their skills improve. Endoscopic simulators are matched to the task

Practice distributed over time yields better learning than compressed practice, in a phenomenon known as the spacing effect[52]. While no studies have evaluated spaced and massed practice directly in endoscopy, a recent trial by Ende *et al*[53] described novice endoscopists performing simulated cases for two hours each week, over a four month period. Trainees who underwent this spaced practice program had superior performance of diagnostic upper endoscopy compared to trainees who practiced on real patients in the 4-mo window[53]. Educators with access to simulators can take advantage of spaced practice principles by introducing booster sessions, which describe training sessions which take place after initial massed training, and just-in-time training, which describe refresher sessions conducted prior to a luminal rotation with a high endoscopic case volume[54-56]. Just-in-time simulation training could also be used to prepare trainees for more complex skills such as polypectomy, whereby trainees 'warm-up' on a simulator before completing the task in real life; a strategy which has been shown to be useful in other procedural domains[57,58].

Another innovative and potentially applicable educational strategy is gamification. Gamification, or the application of game design elements (*e.g.*, points, badges, and leaderboards) to a traditionally nongame contexts (*e.g.*, simulation curricula, learning activity), is increasingly being used within medical education[59,60]. Studies from the broader simulation literature highlight the potential role of gamification as a means to enhance leaner motivation, engagement and procedural skills performance[59,61-64]. For example, MacKinnon *et al*[63] showed that a leaderboard was a positive motivator for simulated CPR practice and Mokadam *et al*[62] used gamification to increase trainees' use of a small-vessel anastomosis simulator, resulting in skills improvement. Game design elements which rank participants, such as leaderboards, are purported to increase learners' sense of control and competence as they enable learners to set attainable process goals[59]. Additionally, gamification can potentially enhance learners' sense of relatedness (interconnectedness with other learners and teachers) which is thought to enhance engagement[59]. While gamification is a potentially useful educational strategy, there is only one study, which is currently in progress, that aims to examine the use of gamification within the endoscopic simulation-based training context[65]. Educators must remember that when integrating gamification, it must be done so purposefully, in that it should align with the learning goals of the simulation-based training to enhance learner motivation and engagement, and ultimately, improve learning[59].

Recently, the concept of immersive virtual reality has been introduced in simulation research. This represents an attempt to improve the realism of simulated settings and increase the user's sense of presence. For example, a recent study in laparoscopic surgery reported on the integration of a virtual reality simulator with a head-mounted display to create an immersive experience in which users have a wide field of view with head tracking and depth perception that more closely represents human vision[66]. The use of such displays has received positive reviews from operating room staff and has been shown to improve response time and performance scores during a simulation of an operating room emergency[67,68]. While studies are needed to assess the learning benefits of immersive virtual reality in endoscopy, the rise of commercially available virtual reality head-mounted displays may allow for

the incorporation of this technology into simulation training programs.

CONCLUSION

Simulation-based training is increasingly being incorporated into endoscopy curricula. Despite its growing use, there remains a need to integrate evidence-based strategies such as deliberate practice with mastery learning, feedback and debriefing, contextual learning, and innovative educational design. Educators looking to implement simulation-based training should consider the specific objectives of training, learner's needs, the magnitude of potential training benefits, and associated costs and prospective savings. When done in a thoughtful and deliberate manner, training programs can maximize the potential learning benefits of simulation.

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MINIREVIEWS

Endoscopic retrograde cholangiopancreatography, lights and shadows: Handle with care

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Abstract

The role of endoscopic retrograde cholangiopancreatography (ERCP) has dramatically changed in the last years, mainly into that of a therapeutic procedure. The treatment of benign biliary disease, like "difficult" choledocolithiasis, with endoscopic papillary large balloon dilation combined with endoscopic sphinterotomy has proven an effective and safe technique. Moreover, safety in ERCP has improved as well, with the prevention of post-ERCP pancreatitis and patient-to-patient transmission of infections. The advent of self-expandable metal stenting has radically changed the management of biliopancreatic malignant strictures, while the role for therapy of benign strictures is still controversial. In addition, cholangioscopy (though the direct visualization of the biliopancreatic ductal system) has allowed for characterization of indeterminate biliary strictures and facilitated rescue therapy of large biliary stones deemed removable. Encouraging data from tissue ablation techniques, such as photodynamic therapy and radiofrequency ablation, need to be confirmed by large sample size clinical controlled trials. On the other hand, we have no drug-coated stents yet available to implant and evidence for the use of biodegradable stents is still weak. The competency and privileging of ERCP and endoscopic ultrasonography have been analyzed longer but the switch between the two procedures, at the same time, is becoming ordinary; as such, the endoscopist interested in this field should undergo parallel edification through training plans. Finally, the American Society for Gastrointestinal Endoscopy's statement on non-anesthesiologist administration of propofol for gastrointestinal endoscopy is not actually endorsed by the European Society of Anaesthesiology,

having many medical-legal implications in some European countries.

Key words: Cholangiopancreatography; Endoscopic papillary large balloon dilation; Self-expandable metal stent; Cholangioscopy; Photodynamic therapy; Radiofrequency ablation; Competency; Privileging; Biodegradable stents; Drug-coated stents

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) has seen radical changes within the last three decades. The development of endoscopic ultrasonography and other imaging technologies has changed the role of ERCP from a diagnostic tool to a unique therapeutic and imaging platform. New technological developments in ERCP for diagnosis and treatment have been slow to progress, thus increasing the necessity of interest in diagnostic and therapeutic fields.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has seen radical changes within the last three decades. The development of endoscopic ultrasonography (EUS) and other imaging technologies has changed the role of ERCP from a diagnostic tool to a unique therapeutic and imaging platform. New technological developments in ERCP for diagnosis and treatment have been slow to progress, thus increasing the necessity of interest in diagnostic and therapeutic fields.

Some critical dilemmas, like the management of "difficult" choledocolithiasis or the decrease of ERCP-related complications like pancreatitis, have been partially solved, while some others remain. For instance, the direct visualization into the biliary tree *via* cholangioscopy (CS) allows for targeted tissue sampling or stone management. The self-expandable metal stent (SEMS) has also dramatically changed the management of biliopancreatic malignant strictures while the role of treatment for benign strictures is still controversial. In addition, emerging alerts from the Food and Drug Administration (commonly referred to as the 'FDA') to a potential association between multidrug-resistant bacteria and duodenoscopes have opened new scenarios to endoscope reprocessing procedures and stimulated the Industry to improve the research in this field as well.

Initially, EUS was introduced as a purely diagnostic procedure. Along with ERCP, technological development has gradually changed the role of EUS to therapeutic application as well. EUS and ERCP share many clinical indications, including equipment and devices, at the same time for the same patient; thus, in a manner greater than their competitors, they are truly complementary, with remarkable ability for mutual aid. This "shared approach" is changing our minds more and more in terms of training and the learning curve. The newly developed ablation therapy, tissue sampling, and endoscopic ultrasound-guided ERCP are leading us into a new dimension, wherein the future biliopancreatic endoscopy might match with genomic research to develop "personalized therapy" for our patients.

This review will critically analyze the big and small steps which have been made since ERCP has been introduced, with a look into the future.

WHAT HAS CHANGED IN THE PAST FEW YEARS?

Management of "difficult" choledocolithiasis

The so-called "difficult stones" are characterized as biliary stones that cannot be extracted easily with a basket or balloon after endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilatation (commonly known as EPBD), mainly due to stone size (diameter > 15 mm), consistency or anatomical variations (*i.e.* postsurgical

anatomy, diverticula, duodenal strictures). In these cases, temporary stent insertion or additional endoscopic procedures, like mechanical lithotripsy or extracorporeal shock wave lithotripsy, are performed with the need of multiple ERCP procedures and eliciting several complications. For these reasons, alternative approaches have been suggested. One of the most frequently used among these is the endoscopic papillary large balloon dilation (EPLBD) combined with EST, as described for the first time by Ersoz *et al*[1] and having a high success rate (90%) in extracting large stones in a single session and low complication rate (16%).

These findings have improved the endoscopist's clinical practice since some features, like large bile duct stones on cholangiography or cross-sectional imaging and distal bile duct strictures, can easily guide our choice on when to perform EPLBD or not. This technique is relatively safe, however careful evaluation of radiological imaging is mandatory since the diameter of the balloon should not exceed the diameter of the distal bile duct and the EPLBD should not be performed when the distal bile duct is not dilated to avoid the risk of perforation[2]. A recent meta-analysis on EST plus EPLBD *versus* EST alone for choledocholithiasis showed fewer overall complications (OR = 0.53, 95%CI: 0.33-0.85, P = 0.008) and decreased use of mechanical lithotripsy (OR = 0.26, 95%CI: 0.08-0.82, P = 0.02) in the EST plus EPLBD group, with no significant differences regarding adverse events and stone clearance[3]. More recently, Hakuta *et al*[4] evaluated short- and long-term outcomes of EPLBD without EST and EPBD for large stones; in a propensity-matched analysis involving 44 patients, EPLBD without EST was significantly more effective for removal of large stones but showed worse long-term outcomes compared to EPBD. EPLBD in patients with periampullary diverticula was found to be safe in a multicentric case series involving four Italian ERCP high-volume centers with complications reported in 8/80 patients and, among these, only 1 severe (duodenal perforation)[5].

CS

CS allows direct visualization of the biliopancreatic ductal system. Initially born as an adjunct procedure performed during surgery or percutaneous transhepatic cholangiography, today CS is mainly performed perorally during ERCP[6]. Different types of CS are possible; the single-operator CS (SOC) with "mother-daughter" cholangioscope (Spyglass™ system, Boston Scientific, Natick, MA, United States) is the most widely used technique and is gradually replacing the first-introduced dual-operator CS. More recently, ultrathin endoscopes have been introduced, permitting a direct peroral CS[7]. The main CS clinical indications include both diagnostic and therapeutic procedures.

The most intriguing of the emerging applications is the characterization of indeterminate biliary strictures. In fact, although ERCP has a high specificity (> 90%) in detecting malignancy, it is burdened by a low sensitivity (about 40%), even when brushing or biopsy is performed[8,9]; in this setting, CS allows a higher - but still not satisfying - diagnostic yield by both the direct endoscopic visualization and bioptic sampling, which is possible during the same procedure. In a recent systematic review including 456 patients among 10 studies, the pooled sensitivity and specificity of SOC-guided biopsies in the diagnosis of malignant strictures were 60.1% and 98%, respectively[10]. Interestingly, the endoscopic visual appearance seems to be more sensitive for malignancy than the targeted biopsies (but at the price of a lower specificity), as determined in the 2011 study by Chen *et al*[11] and subsequently confirmed by the cited review.

The visual impression at CS has emerged as a relevant aid, especially in cases of non-diagnostic brushing or biopsy performed with ERCP (pooled sensitivity and specificity 74.7% and 93.3%, respectively), suggesting a possible role in the diagnostic algorithm. However, there are some major issues to consider. At present, there are no validated imaging criteria for CS, as reflected by the sub-optimal inter-observer agreement[12]; furthermore, some concerns have been raised about the reliability of a diagnosis of malignancy based purely on visual appearance.

The main clinical application currently is the management of difficult biliary stones. CS can be successfully performed after failure of bile duct clearance during ERCP, guiding electrohydraulic or laser lithotripsy; this approach has been shown to be effective and safe, with a success rate ranging from 77% to 96% for dual-operator CS[13-16] and 90% to 100% for SOC[11,17,18]. This evidence has made CS-guided lithotripsy a suitable alternative to EPLBD, as recently evaluated in a randomized controlled trial (RCT) which showed no differences between the two techniques[19]. However, since CS is significantly more expensive than EPLBD, a more reasonable approach could be to limit it to cases of EPLBD failures. Based on the current evidence, we propose an algorithm of endoscopic treatment for common bile duct stones (Figure 1).

Safety in ERCP: prevention of complications and infections

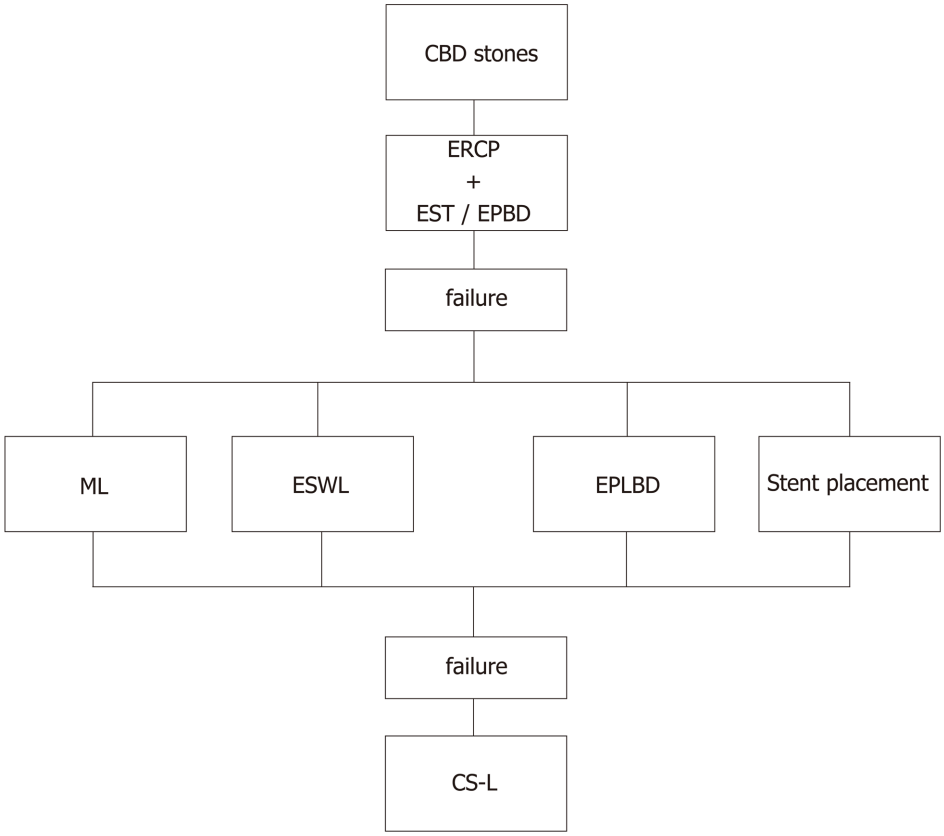

Figure 1 Algorithm of endoscopic treatment for CBD stones. CBD: Common bile duct; CS: Cholangioscopy; CS-L: CS-guided lithotripsy; EPBD: Endoscopic papillary balloon dilatation; EPLBD: Endoscopic papillary large balloon dilation; EST: Endoscopic sphincterotomy; ESWL: Extracorporeal shock wave lithotripsy; ML: Mechanical lithotripsy.

ERCP is associated with several possible complications, including post-procedural bleeding, perforations, pancreatitis and cholangitis; their incidence largely depends on the complexity of the procedure, which can be assessed by various scoring classifications (*i.e*. the American Society for Gastrointestinal Endoscopy (ASGE) grading system)[20,21].

Post-ERCP pancreatitis (PEP) is the most common adverse event in ERCP, with incidence ranging from 3% up to 10%[22]. Since PEP is associated with a significant mortality rate (0.7%) as well as an extended hospitalization rate, strategies to prevent its occurrence have been largely investigated. Among the many possible drugs studied for prophylaxis of PEP, the rectal administration of 100 mg of diclofenac or indomethacin-proposed for the first time by Elmunzer *et al*[23] in 2012 - has been endorsed by European guidelines based on the evidence obtained from four RCTs and three meta-analysis[24].

After this first report, additional evidence about the protective role of nonsteroidal anti-inflammatory drugs (commonly known as NSAIDs) in PEP has been produced but with conflicting results[25-27]. However, two recent meta-analyses confirmed the protective role of NSAIDs for PEP, both carried out in high-risk and average-risk patients[28,29]. In light of these data, both the latest European and American guidelines[22,24] recommend the universal administration of rectal indomethacin in patients undergoing ERCP. To note, there are still variables which need further evaluation, like the best administration route (oral *vs* rectal), timing (before or after the procedure) and patients' selection (high-risk *vs* everyone)[30].

Another prophylactic measure against PEP is an aggressive intravenous hydration. In a 2014 study, Buxbaum *et al*[31] found a significant reduction in PEP incidence among patients receiving hydration with lactated Ringer's solution (3 mL/kg per hr during procedure, 20 mL/kg bolus immediately after, and then 3 mL/kg per hr for 8 hr) *versus* standard hydration (0% *vs* 17%, $P = 0.016$). After this pilot study, more data about the role of lactated Ringer's in this setting have been accumulating. Two recent meta-analyses showed the effectiveness and safety of this strategy[32,33], confirming the promising role of an aggressive hydration protocol for the prevention of PEP.

Apart from pharmacologic prophylaxis, there are other factors which can impact

PEP occurrence. A careful patient selection is fundamental to reducing PEP, whereby ERCP is strictly reserved for patients with high probability of therapeutic intervention[22]. In addition, the cannulation technique seems to play an important role. Wire-guided cannulation, in particular, has been found to significantly reduce PEP compared to the contrast-assisted technique (RR = 0.51; 95%CI: 0.32-0.82)[34]. The use of pancreatic duct stent was evaluated in numerous RCTs and a meta-analysis, which have demonstrated a significant reduction in PEP[35]. Thus, pancreatic duct stent placement is recommended in high-risk patients (repeated inadvertent pancreatic duct cannulation) by international guidelines[22,24].

In 2013, the Centers for Disease Control and Prevention sent an alert to the FDA about a potential association between multidrug resistant bacteria and duodenoscopes. Accurate examinations proved that these cases of infection were occurring despite confirmation that the users were following proper manufacturer cleansing and disinfection or sterilization instructions. For this reason, the FDA implemented a continuous monitoring program on the three manufacturers (Fujifilm Medical Systems USA, Inc, Olympus Medical Systems Corporation, Pentax of America) to warrant appropriate corrective actions.

Duodenoscopes are complex instruments to clean because of the many small working parts, like the elevator channel. If not adequately cleansed and disinfected, tissue or fluid from patients can lead to patient-to-patient transmission of infection. Recently, the Quality Assurance in Endoscopy Committee of the ASGE published a guideline for infection control during gastrointestinal endoscopy with new indications for reprocessing duodenoscopes, including use of double reprocessing cycles and uniform or intermittent surveillance programs with the use of a "culture and hold" policy[36,37]. In a recent systematic review, Olafsdottir *et al*[38] evaluated the correlation between concomitantly sampled adenosine triphosphate and bacterial contamination obtained from the instrument channel and/or elevator mechanism of the duodenoscope, as an alternative method to bacterial culture for evaluating the quality of reprocessing. The authors concluded that current data do not support the direct substitution of adenosine triphosphate for bacterial culture surveillance of duodenoscopes.

Furthermore, corrective actions from manufacturers have been implemented, such as the introduction on the market of new duodenoscopes with a single-use disposable elevator. In the era of single-use devices, like biopsy forceps, snares, sphincterotomes and now disposable elevators, we contemplate the use of "single-patient full equipment kits," so that in the near future we could hope for a single-use duodenoscope too!

Management of malignant and benign biliary strictures

ERCP has a crucial role in the diagnosis and management of cholangiocarcinoma. Tissue sampling from brushing and biopsy has a low sensitivity, ranging from 18% to 60%[39,40]. Hopefully, CS could play a role in the early diagnosis of strictures of uncertain nature, without any evidence of metastasis. If the stricture involves the carrefour or above (Bismuth II-IV), it can be potentially harmful to inject contrast[41] to enhance the intrahepatic tree or try a bilateral drainage though multiple stents placement because of the increased risk of cholangitis[42,43].

Three RCTs have evaluated the outcomes of unilateral and bilateral drainage[43-45]. On one hand, unilateral stenting has higher rates of technical success because it is easier than bilateral stenting and has a significantly lower rate of early complications[43]. On the other hand, recent data suggest that bilateral drainage has a higher clinical success rate, lower re-intervention rate and equivalent technical success rate compared with unilateral drainage[45], due as well to development in SEMS devices and technical improvement. Advanced hilar strictures are challenging to treat for the most of us, and the common feeling is that bilateral drainage fits better with physiological function of the biliary tree. From this prospective, we could might want to reconsider the term of "bilateral and unilateral" as "complete or incomplete" biliary drainage instead (Figure 2). Plastic stents are recommended when a patient's expected survival is < 3 mo, however uncovered SEMSs are cost-effective according to one RCT[44].

Long patency and removability make fully covered (fc)SEMS appealing for therapy of benign biliary stricture (BBS) too, but the high rate of migration dramatically reduces the odds of stricture resolution[46]. For this reason, the Industry have developed a new "anti-migration" designed SEMS. In a recent meta-analysis evaluating the clinical outcome of endoscopic covered metal stenting for the resolution of benign biliary stricture, Zheng *et al*[47] found that the stricture recurrence in a 4-year follow-up was 11% (95%CI: 8%-14%) with the median stents dwelling time of 4.4 mo.

The "multi-stenting" treatment (multiple plastic stenting, insertion of the maximum

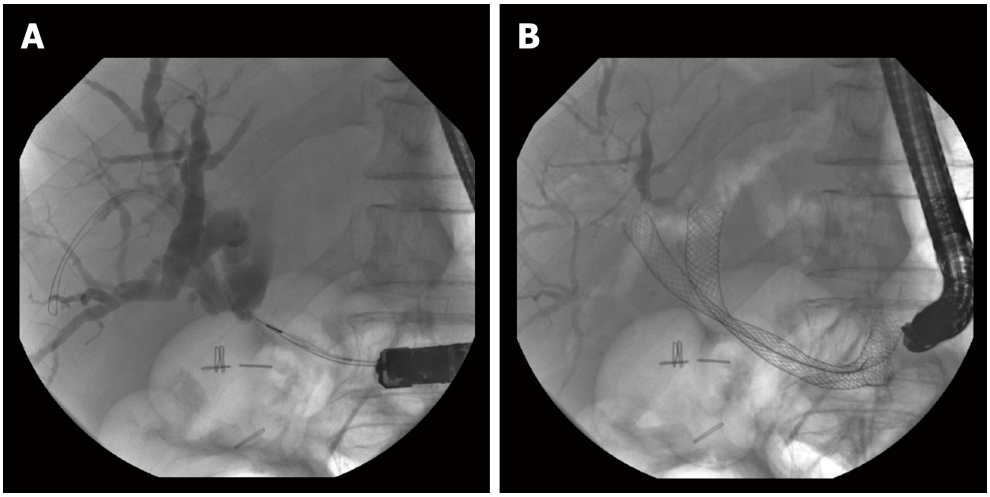

Figure 2 Patient with Klatskin's tumor before (A) and after (B) bilateral or "complete" biliary drainage with uncovered self-expandable metal stent.

number of stents, possible every 3-4 mo, for a total duration of 12 mo; Figure 3) still represents the therapy of choice for BBS[48], especially when related to liver transplantation and post-cholecystectomy injury, while the recommendation to use fcSEMS is still weak. In 2016, Coté *et al*[49] published the results of an RCT regarding the non-inferiority of fcSEMS to plastic stents with respect to stricture resolution. Exclusion criteria were bile duct diameter less than 6 mm and intact gallbladder in whom the cystic duct could be overlapped by a fcSEMS.

Compared with multiple plastic stents (41/48, 85.4%), the resolution rate was 92.6% (50/54) for fcSEMS and the number of ERCPs was significantly lower in the group of fcSEMS *versus* multiple plastic stents (mean, 2.14 *vs* 3.24; mean difference, 1.10; 95%CI: 0.74-1.46; $P < 0.001$), thus indicating that fcSEMS was not inferior to multiple plastic stents after 12 mo in achieving stricture resolution. These data have been recently confirmed in an RCT for anastomotic biliary strictures after liver transplantation[50].

Tringali *et al*[51] recently evaluated fcSEMS removability, stricture resolution rate, and adverse events in 15 patients with chronic pancreatitis and symptomatic main pancreatic duct stricture located in the head. Stent removability from the main pancreatic duct was feasible in all the cases, and 90% of the patients were asymptomatic after 3 yr. The main adverse event was the "*de novo*" stricture that fcSEMS induced in 4 patients (27%), while complete distal migration occurred in 46% of cases. The high clinical efficacy and removability are encouraging results but, on the other side, the high migration rate and the occurrence of fcSEMS–induced strictures suggest further evaluation with RCT to assess the role in this setting.

WHAT COULD POTENTIALLY CHANGE IN THE NEAR FUTURE

Tissue ablation techniques

SEMS occlusion by tissue in-growth frequently occurs with uncovered SEMS inserted to treat hilar cholangiocarcinoma; this may, therefore, require more frequent procedures. The endoscopic goal is for adequate biliary drainage to palliate jaundice, but it also aims to reduce the number of reinterventions. New endoscopic techniques may extend stent patency and patient survival.

Photodynamic therapy (PDT) offers the possibility of tumor mass reduction[52] through the necrosis of the neoplastic tissue due to activation at a specific wavelength of a photosensitizing agent, given intravenously, which accumulates in malignant cells. Many studies have compared outcomes with PDT and biliary stenting *versus* biliary stenting only in palliation of nonresectable cholangiocarcinoma. Recently Moloe and colleagues[53] reported positive effects on biliary drainage, survival and quality of life in patients with advanced cholangiocarcinoma from a systematic review and meta-analysis comparing PDT with biliary stenting *versus* stenting alone. The most common adverse events were cholangitis and phototoxicity. Since cholangitis occurred in all patients with biliary stenting too, it is inappropriate to relate this effect to PDT. These data endorse the promising role of PDT even though limitations exist due to several biases, like small sample size and the heterogeneous methods used for

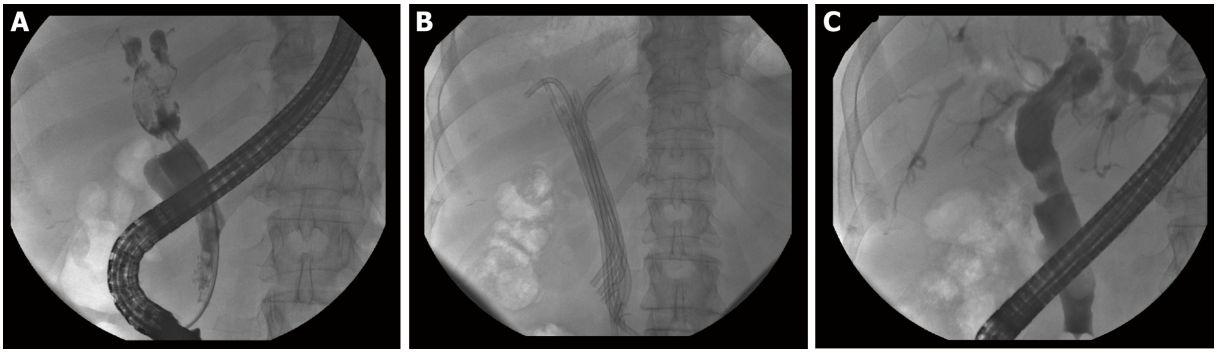

Figure 3 Management of post-cholecistectomy benign biliary stricture. A: Before the treatment; B: Multi-stenting treatment; C: Radiological appearance at the end of treatment.

PDT (percutaneous/endoscopic) and biliary stenting (plastic/SEMS). Well-designed prospective randomized studies are still needed.

The use of SOC for PDT makes the procedure technically more feasible, with shorter fluoroscopy time and longer median survival compared with PDT alone, as reported by Talreja *et al*[54].

Radiofrequency ablation (RFA) has been used historically longer as a heat delivery system for the destruction of primary and secondary hepatic tumors *via* localized coagulative necrosis. Recently, a new probe fit for endoscopic use has become available. A retrospective analysis of patients who have undergone RFA for malignant biliary obstruction has suggested that RFA may prolong survival in patients with advanced cholangiocarcinoma, but these findings need to be confirmed by controlled studies. Moreover, adverse events like pain, cholecystitis, hemobilia and injury to adjacent vascular structures may occur, and this suggests that caution must be taken for the endoscopic-guided use of this technique.

Training in biliopancreatic endoscopy

Competency in advanced procedures such as ERCP and EUS have been long analyzed. For ERCP, selective cannulation in at least 90% of procedures, accurately interpreting endoscopic and radiologic images, and successful sphincterotomy and stent placement are mandatory for the achievement of competency[55,56]. We know that this goal is hard to accomplish for young endoscopists and it takes a long period (according to the latest evidence, 3-yr fellowship or 1 yr of advanced endoscopy training are required[57,58]) and a large amount of procedures (> 200 ERCP under supervision of a tutor, along with 80 sphinterotomies and 60 stent insertions[59]). The EUS learning curve is not easier than that of the ERCP one and includes at least 225 hands-on cases under supervision[60].

In the past few years, simulators have been introduced with the aim of approximating the human anatomy and recreating the difficulties encountered during real-life situations in human patients. Competency-based fellowship programs have spread, to validate trainee assessment as well. In 2018, Wani and colleagues[61] evaluated, in a prospective multicenter cohort study, quality indicator adherence during the first year of independent practice among physicians who completed endoscopic training with a systematic assessment of competence. They used TEESAT (a procedure-specific competence assessment tool with strong validity evidence endorsed by the ASGE) to assess EUS and ERCP skills in a continuous fashion throughout training. At the end of training, overall technical (EUS, 91.7% and ERCP, 73.9%) and clinical (EUS, 91.7% and ERCP, 94.1%) competence were achieved by most of the trainees, thus confirming the effectiveness of training programs.

EUS and ERCP have both evolved from being a diagnostic procedure to a therapeutic procedure. Always more often in our endoscopy rooms, switches from EUS to ERCP or *vice versa* happen. Single-session EUS and ERCP have been shown to be accurate and effective, with minimal complication rates[62].

There are no clear data as to whether a single operator performing both procedures has better outcomes compared to those achieved by two different operators. EUS-guided biliary drainage has emerged as an alternative procedure after failed ERCP and ERCP, but expertise is needed to perform some steps, such as stent insertion. Yet, how many endoscopists can shift from ERCP to EUS is unknown. Maybe this is the time not to consider separate programs of education for learning ERCP and EUS but to instead consider one just for those who are really interested in interventional endoscopy. Endoscopists with experience in both techniques will be increasingly

important, suggesting a parallel formation in training plans for all future endoscopists with an interest in the area.

Biodegradable and drug-coated stents

Therapy with plastic or metallic stent for benign disease requires repeated endoscopy for stent removal. To avoid this, self-expanding biodegradable biliary stents (BDBSs) have recently become available for ERCP. In the past, hyperplasia or restricturing secondary to biodegradable stents encountered in the gastrointestinal stenting for benign diseases limited further use. Several studies on animal and human models to investigate the use of BDBSs with polylactide or polydioxanone in bile ducts showed good biocompatibility of BDBS, with a negligible histologic foreign body reaction and low risk of restricturing[63,64]. Siiki *et al*[63] evaluated the effectiveness and safety of a novel BDBS in 13 patients with iatrogenic cystic duct leaks (n = 7) and BBS (n = 6). Complete bile leak resolution was achieved in all patients and the clinical success rate in BBS was 83% in the median follow-up period of 21 mo (range: 14-25 mo). Repeated MRI during the first year demonstrated the gradual degradation pattern.

These data seem promising, but the small number of cases and the absence of control groups suggest careful evaluation and further controlled studies on long-term clinical results.

Metal stenting for malignant biliary strictures may fail because of tumor ingrowth or overgrowth of excessive epithelial or malignant cells. Drug-coated stents have been used for a long time in coronary artery disease to reduce the incidence of stent malfunction. Only paclitaxel has been trialed in humans with malignant obstruction[65,66] and provided encouraging results. Suk and colleagues[65] found overall patency rates at 3, 6 and 12 mo of 100%, 71% and 36%, respectively, in 21 patients with unresectable malignant biliary strictures treated with metallic stent coated with a paclitaxel-incorporated membrane.

The biggest limit to research in this field is that there are no cheap reproducible models to develop an ideal drug-eluting stent able to inhibit malignant cells growing with reasonable histologic tolerance to the biliary epithelium too.

Sedation in ERCP

ERCP may result in a prolonged procedure requiring adequate sedation.

According to the ASGE statement about non-anesthesiologist administration of propofol for gastrointestinal endoscopy[67], the administration of propofol and standard sedation by non-anesthesiologists is equivalent in terms of efficacy and safety when done in a setting of properly trained staff and accurate patient selection. Moreover, the use of anesthesiologist-administered propofol for selected patients with no risk factors for sedation-related complications is very costly and does not improve safety or procedural outcomes. The long-standing argument among anesthesiologists about the use of propofol by non-anesthesiologists is supported by the absence of an antidote and by the rapid transition from a level of moderate sedation to deep sedation or even general anesthesia, making it therefore unmanageable for a non-anesthesiologist. Moreover, the label indications report that it ''should be administered only by persons trained in the administration of general anesthesia'' and in 2012, the European Society of Anaesthesiology retracted its endorsement to the guideline on non-anesthesiologist administration of propofol for gastrointestinal endoscopy, published together with the European Society of Gastrointestinal Endoscopy and the European Society of Gastroenterology and Endoscopy Nurses and Associates[68]. These issues have deep medico-legal implications, above all in some countries in Europe, that do not make us all have sweet dreams.

CONCLUSION

In the past 30 yr, the role of ERCP has changed deeply.

Radical developments have increased our performance in the diagnostic field, such as with CS, and in the therapeutic field, such as with the advent of SEMS or with the management of "difficult biliary stone" removal. Safety has improved too with the prevention of ERCP-related complications and infections (Table 1).

On the other hand, there are still wide grey areas. We are still far from using biodegradable stents and this means repeating ERCP in patients with benign biliary strictures. Unlike percutaneous therapy of acute myocardial infarction, we have not yet applied drug-coated stent implantation. Even if non-anesthesiologist administration of propofol has been found to be safe in an evidence-based assessment, there is no endorsement from the Anesthesiologists and this can represent a big limitation in some countries.

RFA and PDT are promising tissue ablation techniques; the effect seems to not only

Table 1 Summary of current evidence for each topic

Topic	Current evidence
Management of " difficult" choledocolithiasis	EST plus EPLBD
Cholangioscopy	Electrohydraulic or laser lithotripsy/tissue sampling
Safety in ERCP: complications and infections	
PEP	Rectal administration of 100 mg of diclofenac or indomethacin and pancreatic duct stenting in high-risk and average-risk patients/aggressive intravenous hydration/wire-guided cannulation
Multi-drug resistant bacteria and duodenoscopes	Single-use disposable elevator
Management of malignant and benign biliary strictures	Bilateral drainage for hilar strictures with uSEMS /"multi-stenting" treatment for benign biliary strictures
Tissue ablation techniques	PDT with biliary stenting in advanced cholangiocarcinoma (more studies are needed)
	RFA for advanced cholangiocarcinoma (more studies are needed)
Training in biliopancreatic endoscopy	ERCP: at least 200 procedures under supervision of a tutor with 80 sphincterotomies and 60 stent insertions
	EUS: at least 225 hands-on cases under supervision
Biodegradable and drug-coated stents	BDBSs with polylactide or polydioxanone showed good biocompatibility (more studies are needed)
	Only paclitaxel has been trialed in humans with malignant obstruction (more studies are needed)
Sedation in ERCP	Propofol and standard sedation by non-anesthesiologists is equivalent in terms of efficacy and safety in a setting of properly trained staff and accurate patient selection (ASGE): ESA retracted its endorsement to ESGE and ESGENA

ASGE: American Society for Gastrointestinal Endoscopy; BDBSs: Self-expanding biodegradable biliary stents; EPLBD: Endoscopic papillary large balloon dilation; ESA: European Society of Anaesthesiology; ESGE: European Society of Gastrointestinal Endoscopy; ESGENA: European Society of Gastroenterology and Endoscopy Nurses and Associates; EST: Endoscopic sphincterotomy; PDT: Photodynamic therapy; PEP: Post-ERCP pancreatitis; uSEMS: Uncovered self-expandable metal stent; RFA: Radiofrequency ablation.

be localized but it may prolong the survival of patients with advanced cholangiocarcinoma; however, a large sample size from a controlled study is still needed.

ERCP has given us the chance to directly access the biliary tree and pancreatic duct and this has been a precious achievement, but we have focused our attention to find the best way to treat biliopancreatic disease under the "one size fits all" motto. In the near future, direct visualization and tissue sampling might lead us to understand better the genomic alterations in every single patient, thus allowing for "personalized" targeted molecular therapy.

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ORIGINAL ARTICLE

Retrospective Study

Appropriate number of biliary biopsies and endoscopic retrograde cholangiopancreatography sessions for diagnosing biliary tract cancer

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Fukushima Medical University.

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Abstract

BACKGROUND

Biliary ductal cancer (BDC) is a lethal disease; however, diagnosing BDC is challenging. Biliary biopsies are performed to pathologically diagnose BDC, but the appropriate parameters for biliary biopsy [number of biliary biopsies, number of endoscopic retrograde cholangiopancreatography (ERCP) sessions, *etc*.] are unknown.

AIM

To clarify what constitutes an adequate method for biliary biopsy.

METHODS

In total, 95 patients who underwent endoscopic biliary biopsy without choledochoscopy and who were pathologically diagnosed with BDC were enrolled in this study. The patients were divided into two groups. Seventy-six patients who were diagnosed by biliary biopsy were defined as the positive group (P group), and nineteen patients who were not diagnosed by biliary biopsy were defined as the negative group (N group). The patient characteristics and ERCP-related procedures were compared between the P and N groups.

RESULTS

in the study because the analysis used anonymous clinical data obtained after each patient provided written consent agreeing to treatment. For full disclosure, the details of the study are published on the home page of Fukushima Medical University.

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The numbers of ERCP sessions and biliary biopsies were significantly different between the two groups [ERCP sessions (one/two), P group 72/4 *vs* N group 15/4, *P* value = 0.048; number of biliary biopsies, P group 2 (1-6) *vs* N group 2 (1-7), *P* value = 0.039]. In a multivariate analysis, fewer than 2 ERCP sessions was an independent factor influencing the positivity of the biliary biopsies.

CONCLUSION
This study clarified that ERCP and biliary ductal biopsy should only be performed once. If biliary cancer is not pathologically diagnosed after the first ERCP session, other methods (Endoscopic ultrasonography-guided fine needle aspiration or choledochoscopy-guided biliary ductal biopsy) should be employed.

Key words: Biliary ductal cancer; Biliary biopsy; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasonography-guided fine needle aspiration; Choledochoscopy

Core tip: The appropriate parameters for biliary biopsy [number of biliary biopsies, number of endoscopic retrograde cholangiopancreatography (ERCP) sessions, *etc*.) are unknown. In this report, fewer than 2 ERCP sessions was an independent factor influencing the positivity of the biliary biopsies. If biliary cancer is not pathologically diagnosed after the first ERCP session, other methods (Endoscopic ultrasonography-guided fine needle aspiration or choledochoscopy-guided biliary ductal biopsy) should be employed.

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INTRODUCTION

Biliary ductal cancer (BDC) is a lethal disease; however, diagnosing BDC is challenging. The pathological diagnostic methods for BDC are biliary cytology, biliary brush cytology, and biliary biopsy by endoscopic retrograde cholangiopancreatography (ERCP).

The sensitivity of biliary cytology for diagnosing malignant biliary strictures is reported to be 32%-57%[1-9], and the sensitivity of biliary brush cytology is 33%-58%[3,4,10,11]. The sensitivity of biliary biopsy for diagnosing malignant biliary strictures is reported to be 36%-81%[3,4,7,9,11-13]. All reports except two indicate that the sensitivity of biliary biopsy is less than 65%. The sensitivities of biliary brush cytology and biliary biopsy are 61%-70.4%[4,11]. In addition, the sensitivity of repeated biliary cytology by endoscopic nasobiliary drainage tube is reported to be 72.4%[14].

Of these procedures for diagnosing BDC, the appropriate method of biliary biopsy is not clearly defined. In particular, the correct number of biliary biopsies is unknown, as is whether additional ERCP sessions are appropriate if the first session does not result in the pathological diagnosis of BDC. Therefore, the aim of this study was to clarify the appropriate parameters for biliary biopsy for the diagnosis of BDC.

MATERIALS AND METHODS

Ethics

This study was a retrospective study conducted to determine the adequate parameters for biliary biopsy used to diagnose BDC. Informed consent was not required for this study because the analysis utilized anonymous clinical data that were obtained after each patient agreed to treatment by providing written informed consent. This study

was approved by the Institutional Review Board of Fukushima Medical University.

Subjects and methods of diagnosing BDC

We enrolled 95 patients who underwent endoscopic biliary biopsy without choledochoscopy and who were pathologically diagnosed with BDC between February 2007 and March 2018. These patients underwent ERCP and biliary cytology or brush cytology and biliary biopsy. If they were not diagnosed by ERCP-related procedures, they were diagnosed by endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA), biopsy from duodenal invasion, or biopsy using choledochoscopy. The patients were divided into two groups. Seventy-six patients who were diagnosed by biliary biopsy were defined as the positive group (P group). Nineteen patients who were not diagnosed by biliary biopsy were defined as the negative group (N group).

Procedures for endoscopic biliary biopsy

In all patients, an endoscope was inserted after they were sufficiently sedated with midazolam. After the endoscope reached the descending part of the duodenum, the biliary cannulation was started. If the biliary cannulation was successful, bile was collected for biliary cytology. After a range of malignant biliary strictures were confirmed by cholangiography, endoscopic sphincterotomy (EST) or intraductal ultrasonography, biliary brush cytology was performed if deemed appropriate. At this stage, biliary biopsy was performed to diagnose the malignancy or the status of BDC progression. The number of biliary biopsies was determined randomly by each endoscopist. The collection of a sufficient specimen was visually confirmed. If a patient had already received a biliary stent, the stent was removed before biliary cannulation. In five patients, endoscopic nasobiliary drainage (ENBD) was performed. The bile that was used for cytology was turned in the pathological department twice a day for three days. JF260V, JF240, and TJF240 ERCP endoscopes (Olympus, Tokyo, Japan) were used. An MTW ERCP catheter taper (MTW Endoskopie, Wesel, Germany), Tandem XL (Boston Scientific Japan, Tokyo, Japan) or PR-233Q (Olympus) was used as the ERCP catheter. A Clever Cut 3V or an RX Needle Knife (Boston Scientific Japan, Tokyo, Japan) were used for endoscopic sphincterotomy (EST). An Endo Jaw FB231K (Olympus) or a Radial Jaw™ 4 Biopsy Forceps (Boston Scientific Japan) was used for the biliary biopsy (Figure 1). If the biliary stricture was too tight to allow the insertion of the Radial Jaw, a SpyBite (Boston Scientific Japan, Tokyo, Japan) was used for the biliary biopsy. Reverse α-type or α-type ENBD catheters (Gadelius Medical, Tokyo, Japan) or a Flexima™ Nasobiliary Catheter single pigtail (Olympus) was used for the ENBD catheter. The choledochoscope used in this study was a SpyGlass DS™ (Boston Scientific Japan).

Examined items

Patient characteristics (age, gender, receipt of antithrombotic drugs, location of tumor, Union for International Cancer Control (UICC) stage, cholangitis within the last month) and ERCP-related procedures (number of ERCP sessions; diagnosability of BDC from bile, brush cytology or ENBD cytology; EST; cup diameter of biopsy forceps (1 mm or 2 mm); total biopsy number; biopsy number before biliary stenting; biopsy number after biliary stenting; adverse events; post-ERCP pancreatitis (PEP)) were compared between the P group and the N group. Cholangitis was diagnosed according to the presence of an elevated white blood cell (WBC) count or C-reactive protein (CRP) level (WBC ≥ 10000/μL or CRP ≥ 5 mg/dL). The biopsy number was defined as the number of biopsies taken from the main stricture of the biliary cancer minus the number of screening and mapping biopsies. PEP was diagnosed by the presence of hyperamylasemia more than three times the normal level more than 24 hours after ERCP and abdominal pain[15]. In addition, we confirmed peripancreatic inflammation by contrast CT imaging in all PEP patients. The seriousness of PEP was determined according to the consensus guidelines proposed by Cotton *et al*[15] (mild: planned hospitalization was prolonged by 2-3 d, moderate: planned hospitalization was prolonged by 4-10 d, severe: planned hospitalization was prolonged by more than 10 d, a pseudocyst was present, intervention (percutaneous drainage or surgery) was necessary, or hemorrhagic pancreatitis developed).

Statistical analyses

The Mann-Whitney *U* test was used for the comparisons of continuous and ordinal variables. Fisher's exact test was used for the comparisons of nominal variables. Multivariate logistic regression analysis was used. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the EZR platform (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna,

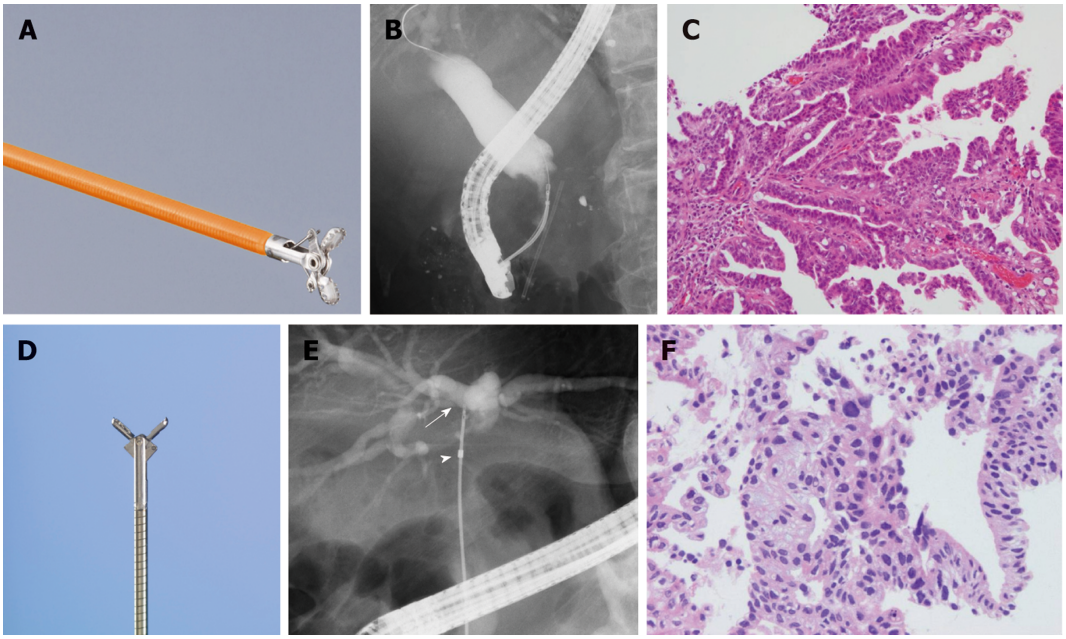

Figure 1 Biliary biopsy forceps and the procedural steps of biliary biopsies. A: Radial Jaw™ 4 Biopsy Forceps. The cup diameter of these forceps is 2 mm. B: The image perspective in cholangiography. Biliary biopsy was performed with a Radial Jaw™ 4. C: The specimen was obtained with 2-mm biopsy forceps (X 200, hematoxylin eosin (HE) staining). Papillate lines were formed by biliary cancer cells. D: SpyBite. The cup diameter of these forceps is 1 mm. E: Biliary biopsy was performed with the SpyBite system through the MTW endoscopic retrograde cholangiopancreatography (ERCP) catheter (arrow: the tip of a SpyBite, arrowhead: the tip of an MTW ERCP catheter). F: The specimen was obtained by 1-mm biopsy forceps (X 400, HE stain). Papillate lines were formed by columnar biliary cancer cells.

Austria). More precisely, EZR is a modified version of R commander that was designed to perform functions that are frequently used in biostatistics[16].

RESULTS

Regarding patient characteristics, no items except age were significantly different between the P group and N group (Table 1). Age was significantly higher in the P group than in the N group [P group 75 (29 - 90) years *vs* N group 68 (43-82) years, *P* value = 0.012; median (range)].

Regarding ERCP-related procedures, the number of ERCP sessions and the total number of biopsies were significantly different between the two groups (ERCP session (one/two), P group 72/4 *vs* N group 15/4, *P* value = 0.048; total number of biopsies, P group 2 (1-6) *vs* N group 2 (1-7), *P* value = 0.039) (Table 2).

In univariate analysis, only fewer than two ERCP sessions significantly influenced the positivity of biliary biopsies (Table 3). In multivariate analysis including two factors (total number of biopsies ≤ 1, number of ERCP sessions < 2; the *P* values of these two factors were lower than the others in univariate analysis), fewer than two ERCP sessions was the independent factor influencing the positivity of biliary biopsies (Table 4).

DISCUSSION

In this study, we verified an adequate method of biliary biopsy for the diagnosis of BDC. Although the number of biliary biopsies did not affect the positivity of the biliary biopsies, it was revealed that multiple ERCP sessions for the diagnosis of BDC were not useful. If the result of the biliary biopsy is negative after the first ERCP session, other methods should be subsequently employed.

In past reports, EUS-FNA and choledochoscopy were introduced as additional methods. The efficacy of EUS-FNA for diagnosing malignant biliary strictures was reported in previous studies. The sensitivity of EUS-FNA for the diagnosis of malignant biliary strictures is 45%-94.0% with a specificity of 77%-100% and an accuracy of 68%-94.0%[17-23]. Ohshima *et al*[24] reported that 10 bile duct cancer cases not diagnosed by ERCP (brush cytology and biopsy) were successfully diagnosed by EUS-FNA. Nayar *et al*[25] and DeWitt *et al*[23] reported that EUS-FNA was successful after poor results were obtained with ERCP-related diagnostic methods. In addition,

Table 1 Comparison of patient characteristics between the positive group and the negative group

	P group (*n* = 76)	N group (*n* = 19)	*P* value
Age (yr)	75 (29-90)	68 (43-82)	0.012
Males	60 (78.9)	12 (63.2)	0.229
Received antithrombotic drugs	14 (18.4)	0 (0)	0.064
Location of tumor (distal/hilar)	45/31	8/11	0.205
UICC stage (1/2/3/4)	27/29/10/10	7/7/3/2	0.91
Cholangitis within the last month	10 (13.2)	3 (15.8)	0.719

The values are shown as the median (range) or *n* (%). P: Positive; N: Negative; UICC: Union for International Cancer Control.

malignant lymph node swelling in pancreaticobiliary tract cancers were successfully diagnosed by EUS-FNA[26,27].

Starting approximately ten years ago, SpyGlass® (Boston Scientific Japan, Tokyo, Japan) has been increasingly used as the preferred choledochoscope. SpyGlass® was introduced in 2006 and is a very thin reusable fiber that is used with a disposable delivery catheter (SpyScope®, Boston Scientific Japan, Tokyo, Japan), which can be moved in four directions. The SpyGlass® system can be controlled by a single operator. In a systematic review by Navaneethan *et al*[28], the sensitivity and specificity of biliary biopsy with the SpyGlass® system were 74.7% and 93.3%, respectively, for the diagnosis of malignant biliary strictures that had previously failed to be diagnosed by brushings or biopsy[28-32]. In addition, a patient with an indeterminate biliary stricture who was not diagnosed by ERCP (brush cytology, intraductal biopsy) or EUS-FNA was diagnosed with cholangiocarcinoma by SpyGlass®-guided biopsy[33]. Recently, an advanced version of SpyGlass®, SpyGlass® DS (Boston Scientific Japan, Tokyo, Japan), was released. The image transmitted by SpyGlass® DS is clearer than the image transmitted by the original SpyGlass®, and the delivery system for SpyGlass® DS is easier to operate than that of SpyGlass®. The efficacy of SpyGlass® DS-guided biliary biopsy for the diagnosis of malignant biliary strictures that remained undiagnosed by previous brush cytology, biliary biopsy or EUS-FNA has been reported[34,35].

Then, the diagnostic methods used in the 19 patients in the N group were considered; 10 patients were diagnosed via surgery, 4 were diagnosed after bile cytology, 2 were diagnosed via biliary brush cytology, 1 was diagnosed through choledochoscopy-guided biopsy, 1 was diagnosed via EUS-FNA of metastatic lymph nodes, and 1 was diagnosed via a biopsy from duodenal invasion. Bile cytology and biliary brush cytology were performed with biliary biopsy. In addition, 3 of the 4 patients who underwent 2 sessions of ERCP remained undiagnosed before surgery. Therefore, other methods, such as EUS-FNA or choledochoscopy-guided biliary biopsy, should be performed if biliary cancer is not diagnosed in the first ERCP session.

This study had some limitations. First, this study was performed with a small sample size and at a single institution. Thus, a statistical bias might exist. Second, this study was retrospective. Therefore, the indications regarding the volumes of the specimens sampled by biliary biopsies were absent except for visually confirming the presence of a sufficient specimen. In the future, a larger sample size and prospective multicenter study are needed. Third, the volumes of the specimens sampled by biliary biopsy were not assessed. The correlation between the pathological diagnosis and the volume of biliary cancer specimens should be verified.

In conclusion, this study clarified that ERCP for biliary ductal biopsy should only be performed once. If biliary cancer is not pathologically diagnosed after the first session of ERCP, other methods (EUS-FNA or choledochoscopy-guided biliary ductal biopsy) should be employed.

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Table 2 Comparison of endoscopic retrograde cholangiopancreatography -related procedures between the positive group and the negative group

	P group (*n* = 76)	N group (*n* = 19)	*P* value
Number of ERCP sessions (1/2)	72/4	15/4	0.048
EST	74 (97.4)	17 (89.5)	0.177
Diagnosability of bile or brush or ENBD cytology	16/68[1] (23.5)	5/19 (26.3)	0.77
Cup diameter of biopsy forceps (1 mm/2 mm)	8/68	2/17	1.0
Total number of biopsies	2 (1 - 6)	2 (1 - 7)	0.039
Number of biopsies before biliary stenting	2 (1 - 4)	2 (1 - 3)	0.119
Number of biopsies after biliary stenting	2 (1 - 4)	1 (1 - 6)	0.065
PEP	4 (5.3)	0 (0)	0.58
Moderate	2		
Severe	2		

[1]Biliary cytology, brush cytology and endoscopic nasobiliary drainage cytology were not performed in 8 patients in the P group. The values are shown as median (range) or *n* (%). ERCP: Endoscopic retrograde cholangiopancreatography; P: Positive; N: Negative; EST: Endoscopic sphincterotomy; ENBD: Endoscopic nasobiliary drainage; PEP: Post-ERCP pancreatitis.

Table 3 Univariate analysis of biliary biopsy positivity

	P group (*n* = 76)	N group (*n* = 19)	*P* value
Total number of biopsies ≤ 1	32 (42.1)	4 (21.1)	0.116
Total number of biopsies ≤ 2	62 (81.6)	12 (63.1)	0.120
Total number of biopsies ≤ 3	69 (90.8)	15 (78.9)	0.222
Number of ERCP sessions < 2	72 (94.7)	15 (78.9)	0.048

The values are shown as *n* (%). P: Positive; N: Negative; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Multivariate stepwise analysis of biliary biopsy positivity

	OR	95%CI	*P* value
Number of ERCP sessions < 2	4.8	1.08-21.4	0.04

OR: Odds ratio; CI: Confidential interval; ERCP: Endoscopic retrograde cholangiopancreatography.

ARTICLE HIGHLIGHTS

Research background

Biliary ductal cancer (BDC) is a lethal disease; however, the histological diagnosis of BDC is difficult.

Research motivation

Histological diagnosis of BDC is achieved by endoscopic biliary biopsy except for surgery. However, the appropriate method (*i.e.*, the number of times, the number of ERCP sessions) for biliary biopsy is unknown.

Research objectives

This study aims to clarify the appropriate method of endoscopic biliary biopsy.

Research methods

The subjects of this study were patients who were histologically diagnosed with BDC. The patients who could be diagnosed by biliary biopsy were determined as the positive group (P group), and the patients who could not be diagnosed by biliary biopsy were determined as the negative group (N group). The methods for ERCP procedures were compared between the P group and the N group.

Research results

Multiple ERCP sessions did not contribute to the improvement of the diagnosability of biliary biopsy.

Research conclusions

If biliary cancer is not pathologically diagnosed after the first session of ERCP, other methods should be employed.

Research perspectives

From the results of this study, several methods will be developed and tested for diagnosing BDC.

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META-ANALYSIS

Treatment of high-grade dysplasia and intramucosal carcinoma using radiofrequency ablation or endoscopic mucosal resection + radiofrequency ablation: Meta-analysis and systematic review

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Abstract

BACKGROUND

The progression of Barrett's esophagus (BE) to early esophageal carcinoma occurs sequentially; the metaplastic epithelium develops from a low-grade dysplasia to a high-grade dysplasia (HGD), resulting in early esophageal carcinoma and, eventually, invasive carcinoma. Endoscopic approaches including resection and ablation can be used in the treatment of this condition.

AIM

To compare the effectiveness of radiofrequency ablation (RFA) *vs* endoscopic mucosal resection (EMR) + RFA in the endoscopic treatment of HGD and intramucosal carcinoma.

METHODS

In accordance with PRISMA guidelines, this systematic review included studies comparing the two endoscopic techniques (EMR + RFA and RFA alone) in the

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treatment of HGD and intramucosal carcinoma in patients with BE. Our analysis included studies involving adult patients of any age with BE with HGD or intramucosal carcinoma. The studies compared RFA and EMR + RFA methods were included regardless of randomization status.

RESULTS
The seven studies included in this review represent a total of 1950 patients, with 742 in the EMR + RFA group and 1208 in the RFA alone group. The use of EMR + RFA was significantly more effective in the treatment of HGD [RD 0.35 (0.15, 0.56)] than was the use of RFA alone. The evaluated complications (stenosis, bleeding, and thoracic pain) were not significantly different between the two groups.

CONCLUSION
Endoscopic resection in combination with RFA is a safe and effective method in the treatment of HGD and intramucosal carcinoma, with higher rates of remission and no significant differences in complication rates when compared to the use of RFA alone.

Key words: Barrett esophagus; Radiofrequency; Endoscopic mucosal resection; HALO system

Core tip: This study is important for providing a framework for an endoscopic intervention that can prevent the progression of Barrett's esophagus (BE) into early esophageal carcinoma. This meta-analysis aims to compare two endoscopic techniques, namely, radiofrequency ablation by the HALO system (RFA) alone and RFA in combination with an endoscopic resection (EMR+RFA), in the treatment of high-grade dysplasia and intramucosal carcinoma in patients with BE. It also aims to evaluate the efficiency of each treatment and the prevalence of adverse events.

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INTRODUCTION

The progression of Barrett's esophagus (BE) to early esophageal carcinoma occurs sequentially; the metaplastic epithelium develops from a low-grade dysplasia (LGD) to a high-grade dysplasia (HGD), resulting in early esophageal carcinoma and, eventually, invasive carcinoma[1,2]. According to several randomized studies, endoscopic interventions can prevent the progression of the disease[2,3].

Esophagectomy has been the treatment for BE that is associated with HGD or early esophageal carcinoma, and it has been recommended prior to endoscopic ablation; however, the procedure is associated with high rates of morbidity and mortality. In an attempt to avoid the complications associated with an esophagectomy, endoscopic therapies have been developed to treat early lesions[4].

BE may be treated endoscopically by using resection techniques (such as endoscopic mucosal resections and endoscopic submucosal resections) and ablative techniques (such as radiofrequency ablations, photodynamic therapies, and argonium plasma coagulations). The most common resection techniques use CAP (Olympus) and the Duette Kit (W. Cook). An endoscopic resection is considered to be a method with a high diagnostic accuracy and therapeutic efficacy[5], with the advantage that it also enables the histopathological study of the resected mucosa. Either localized or circumferential resections can be performed, though circumferential resections have greater morbidities.

Radiofrequency ablation, the most widely used technique in recent years, uses the HALO 360 system for circumferential ablations and the HALO 90 system for focal ablations (BARXX Medical, Sunnyvale, California). The first major study on RFA was conducted from 2003 to 2005 in eight centers in the USA by Sharma *et al*[6]. In this study, only patients with BE without dysplasia were included, and Sharma *et al*[6] reported a 70% success rate in eradicating intestinal metaplasia. Subsequent studies included patients with LGD, with remissions reported in 100% of the cases[6]. Later studies, which included patients with HGD and intramucosal carcinoma, also reported favorable success rates[7].

The combination of resection techniques with ablative techniques is now a form of treatment in cases where there are visible macroscopic lesions, since it is believed that these regions contain more advanced stages of the disease. The resection of the macroscopic lesions enables histopathological studies that more precisely define the degree of mucosal invasion.

The aim of this meta-analysis is to compare radiofrequency ablation (RFA) and endoscopic mucosal resection (EMR) + RFA in the treatment of HGD and intramucosal carcinoma in patients with BE; specifically, the meta-analysis compared the efficacy and the prevalence of adverse events in each treatment.

MATERIALS AND METHODS

The current study was registered in PROSPERO (CRD42016049780) and was designed by using PRISMA guidelines[8]. Our analysis included studies involving adult patients of any age with BE and HGD or intramucosal carcinoma. These were comparative studies involving RFA using the Halo technique (BARXX Medical, Sunnyvale, California), either with or without the use of an endoscopic resection, in patients with BE. Studies were included regardless of randomization status. We included papers without language restrictions and that used full-text versions of the articles.

Electronic databases, such as MEDLINE, Scopus, and LILACS, were searched, along with a search of the gray literature. The following search strategies were used in MEDLINE: (1) (BARRETT ESOPHAGUS OR BARRETT'S ESOPHAGUS) AND (CATHETER ABLATION OR RADIOFREQUENCY) and (2) (esophagus neoplasm OR esophageal neoplasm OR esophagus cancer) AND (catheter ablation OR radiofrequency). In the other databases, the strategies used were (BARRETT ESOPHAGUS OR BARRETT'S ESOPHAGUS) AND (CATHETER ABLATION OR RADIOFREQUENCY).

Two independent reviewers selected the studies for the meta-analysis and, in cases of disagreement; the issues were addressed by utilizing a scientific methodology discussion group until a consensus was reached.

The arms of the study included a mucosal resection, followed by RFA (intervention), and RFA alone (control). The expected outcomes included the complete remission of the HGD and intramucosal carcinoma, as determined by endoscopic and histological evaluations. Complications, such as bleeding, perforations, thoracic pain, and stenosis resulting from the procedures, were also noted.

Since the included studies were observational studies, the NewcastleOttawa scale was used. This scale evaluates the quality of the studies by analyzing the following factors: selection of the exposed and unexposed cohorts, the exposure method, the demonstration that the outcome of interest was not present before the start of the study, the comparability between the cases *vs* the controls, the assessment of the outcome, the demonstration that the follow-up was long enough to evaluate the outcome, and the adequacy of the follow-up. Studies with a score of ≥ 6 were included[9]. Studies that presented losses of > 20% were excluded.

The RevMan5 software (Review Manager Version 5.3.5 - Cochrane Collaboration, Copyright © 2014) was used for the meta-analysis of the outcomes. Heterogeneity was modified by up to 50%, with an analysis of sensitivity where it was possible and necessary. In addition, the difference between the samples was calculated as the risk difference for the dichotomous variables with a Cochran–Mantel–Haenszel test, with a confidence interval of 95%.

RESULTS

The search strategy used in the MEDLINE database led to the retrieval of 418 articles by using the first search technique and 368 by using the second technique. Another 373 articles were retrieved from the Scopus database, and 323 were retrieved from the

LILACS database, but all of these articles were included in the MEDLINE search.

Initially, eight papers[10-17] were selected that compared RFA alone to RFA with an endoscopic resection for the treatment of HGD and intramucosal carcinoma, thus leading to an initial total of 2016 patients (Table 1). One study by Phoa *et al*[13] had to be excluded because the data could not be extracted for the meta-analysis. The seven papers that were included represented a total of 1950 patients, with 742 in the ablation with endoscopic resection group, and 1208 in the RFA alone group (Figure 1).

Eradication of HGD, stenosis, bleeding, and thoracic pain were analyzed

Eradication: All seven selected studies evaluated the eradication of HGD and intramucosal carcinoma, and it was possible to submit all of the data for a meta-analysis, on the basis of the absolute numbers. Efficacy was evaluated at ≥ 12 months after the start of treatment. The follow-up times varied among the studies (9-32 mo), and there were differences in the follow-up times between the study arms in several studies.

According to the analysis, there was a significant difference between the two groups [RD 0.35(0.15, 0.56)], with better results observed in the patients who underwent endoscopic resections and RFA (EMR + RFA). The heterogeneity was high (I 2: 95%) and was not related to publication bias. The random model was used (Figure 2).

Stenosis: It was possible to analyze the data for all seven studies[10-17]. The cases of stenosis that occurred at any time during the treatment were included. According to the analyses, there was no significant difference between the two groups [RD 0.03 (0.00, 0.05)]. The heterogeneity was moderate (I 2: 39%) and was not related to publication bias. The fixed model was used (Figure 3).

Bleeding: Only four studies provided information for the meta-analysis on bleeding: Li *et al*[10], Kim *et al*[14], Calloil *et al*[15], and Pouw *et al*[17]. According to the data, there was no significant difference between the two groups [SD 0.0 (−0.01, 0.02)], with low heterogeneity (I 2: 18%). The fixed model was used (Figure 4).

Thoracic pain: Only two studies provided data on the outcome of thoracic pain: Okoro *et al*[16] and Pouw *et al*[17]. According to the analysis, there was no significant difference between the two groups [SD -0.04 (-0.22, 0.13)]. The heterogeneity was high (I 2: 62%) and was not related to publication bias. The random model was used (Figure 5).

DISCUSSION

In all of the studies that were used in this meta-analysis, resections were performed if there were visible lesions or mucosal irregularities in the esophagogastric junction. In some cases, rescue EMRs were necessary during the follow-ups.

When regarding the eradication of HGD and intramucosal carcinoma, the use of resection with RFA was significantly more effective than RFA alone. In five cases, the combination of the techniques had an efficacy of > 90% (90%-100%)[10-12,15,17]. It was necessary to maintain high heterogeneity across the studies in the meta-analysis (95%) because many of the studies were lost to analysis when the sensitivity tests were performed.

Although the vast majority of the individual studies report that there is no difference between the groups of patients[11,12,15,16], some of the studies discuss the fact that the patients who were submitted to resection before ablation were more frequently diagnosed with intramucosal carcinoma than with HGD (66% *vs* 43%)[11], *i.e.*, the patients were at a more advanced stage of the disease; therefore, they had a greater chance of incomplete resection or recurrence.

In 2016, Qumseya *et al*[18] published a systematic review comparing the complication rates of RFA and RFA associated with EMR. An overall complication rate of 8.8% was observed, with a 4.4% (P = 0.015) higher rate in the group that underwent RFA + EMR. The complications included: 5.6% who had strictures, 1% who had bleeding, and 0.6% who had perforations. These data are similar to those observed in the present study.

Another systematic review performed by Qumseya *et al*[19] in 2017, which included 2746 patients and evaluated the progression of LGD in patients with BE who underwent radiofrequency ablation and with surveillance only, showed a risk reduction of 10.9% in favor of the group submitted to RFA.

Regarding the eradication of metaplasia, the studies of Kim *et al*[14] and Caillol *et al*[15] demonstrated higher rates of incomplete treatment (remission of metaplasia) in

Table 1 Characteristics of the studies included in the endoscopic mucosal resection + radiofrequency ablation arms *vs* radiofrequency ablation alone

Ref.	Country	Centers	Type of study	Subjects (EMR + RFA/RFA alone	Outcomes
Li *et al*[10], 2015	USA	148	Observational retrospective	1263 (406/857)	Efficacy and safety
Strauss *et al*[11], 2014	USA	2	Observational retrospective	36 (31/5)	Efficacy and safety
Haidry *et al*[12], 2013	England	19	Observational retrospective	335 (164/171)	Efficacy and safety
Kim *et al*[14], 2012	USA	1	Observational retrospective	169 (65/104)	Efficacy and safety
Caillol *et al*[15], 2012	France	1	Observational retrospective	34 (16/18)	Efficacy and safety
Okoro *et al*[16], 2012	USA	1	Observational retrospective	100 (44/46)	Efficacy and safety
Pouw *et al*[17], 2008	The Netherlands	1	Observational retrospective	44 (31/13)	Efficacy and safety

EMR: Endoscopic mucosal resection; RFA: Radiofrequency ablation.

patients who were submitted to ablation by radiofrequency alone. The rates of incomplete treatment ranged from 12% to 44% in the group submitted to resection, compared to 22% to 56% in the groups submitted to RFA alone. Although there was no significant difference between the two groups in relation to the incomplete remission of metaplasia (64% for both), Li *et al*[10] reported that 3.6% of patients who underwent RFA alone eventually progressed to having invasive adenocarcinoma, compared with 1.5% in the EMR + RFA group.

In relation to complications, four types of complications were reported in the studies: stenosis, bleeding, perforations, and thoracic pain. However, only three of these types could be analyzed because only one study cited numerical data on perforations[17], with one case occurring after the endoscopic resection. Other studies have reported that perforations did not occur in either of the two groups[10,12,16].

Our meta-analysis did not show any significant difference in the prevalence of stenosis, bleeding, or thoracic pain between the two groups. Only the study conducted by Kim *et al*[12] showed a higher number of stenosis cases in the RFA alone group, compared to the EMR + RFA group (7.7% *vs* 4.6%).

The strong points of this work are as follows: there are no systematic reviews comparing EMR + RFA *vs* RFA alone; although the studies used were observational studies, all of the studies had a score > 5 on the Newcastle-Ottawa Scale, *i.e.*, good methodological quality; and the review had a large sample size, with 1971 patients in total (Table 2).

In all of the studies included in this systematic review, the pathological samples were evaluated by at least two pathologists to confirm the presence of HGD and intramucosal carcinoma, with the exception of Li *et al*[10], wherein only one pathologist reviewed the samples.

One limitation of this systematic review is the heterogeneity of the techniques used to perform the endoscopic resections. The majority of the studies only cite the techniques without quantifying them, as shown in Table 3 There is also a lack of information about the techniques used to diagnose residual BE, which is also shown in Table 3.

The presence of buried glands after RFA is an obscure topic in the literature, likely due to the difficulty of diagnosing this condition. Sharma *et al*[6] evaluated 3007 neosquamous biopsies after RFA, and no buried glands were reported. In a systematic review conducted by Gray *et al*[20], buried metaplasia was found in 9 patients out of 1004 (0.9%). The other studies included in this systematic review did not report on the diagnosis of buried glands.

The weak points relate to the fact that few studies have compared the two groups and that the studies included nonconsecutive patients. There were no randomized studies that compared endoscopic resections and RFA with RFA alone because the patients who presented visible changes during endoscopies (nodularities or other lesions) were submitted for resections and could not be treated exclusively by ablative methods. Moreover, only three studies presented optimal follow-up periods (> 24 mo) to evaluate the eradication of the disease.

In conclusion, endoscopic resection, in combination with RFA, is a safe and effective method in the treatment of HGD and intramucosal carcinoma, with higher rates of remission and no significant difference in complication rates when compared to RFA alone.

Table 2 Newcastle-Ottawa Scale for evaluating the quality of the studies

Ref.	Selection				Comparability	Outcome			Points
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohort	
Li *et al*[10], 2015	×	×	×	×	×	×	×		7 Points
Strauss *et al*[11], 2014	×	×	×	×	×	×	×	×	8 Points
Haidry *et al*[12], 2013	×	×	×	×	×	×		×	7 Points
Kim *et al*[14], 2012	×	×	×	×	×	×			6 Points
Caillol *et al*[15], 2012	×	×	×	×		×		×	6 Points
Okoro *et al*[16], 2012	×	×	×	×	×	×		×	7 Points
Pouw *et al*[17], 2008	×	×	×	×	××	×		×	8 Points

Table 3 Endoscopic resection and residual Barrett's esophagus diagnosis methods

Ref.	Endoscopic resection method	Residual BE diagnosis method
Li *et al*[10], 2015	Not mentioned	Not mentioned
Strauss *et al*[11], 2014	Duette device	Not mentioned
Haidry *et al*[12], 2013	Duette device	Not mentioned
Kim *et al*[14], 2012	ER-cap technique (Olympus) (55%); Duette device (45%)	NBI assisted
Caillol *et al*[15], 2012	Duette device or double channel technique	Staining with acetic acid or high definition endoscopy
Okoro *et al*[16], 2012	ER-cap technique (Olympus) and Duette device*	Not mentioned
Pouw *et al*[17], 2008	ER-cap technique (Olympus) and Duette device*	Lugol's staining (2%) or narrow-band imaging[1]

[1]Authors did not mention which method was used. BE: Barrett's esophagus.

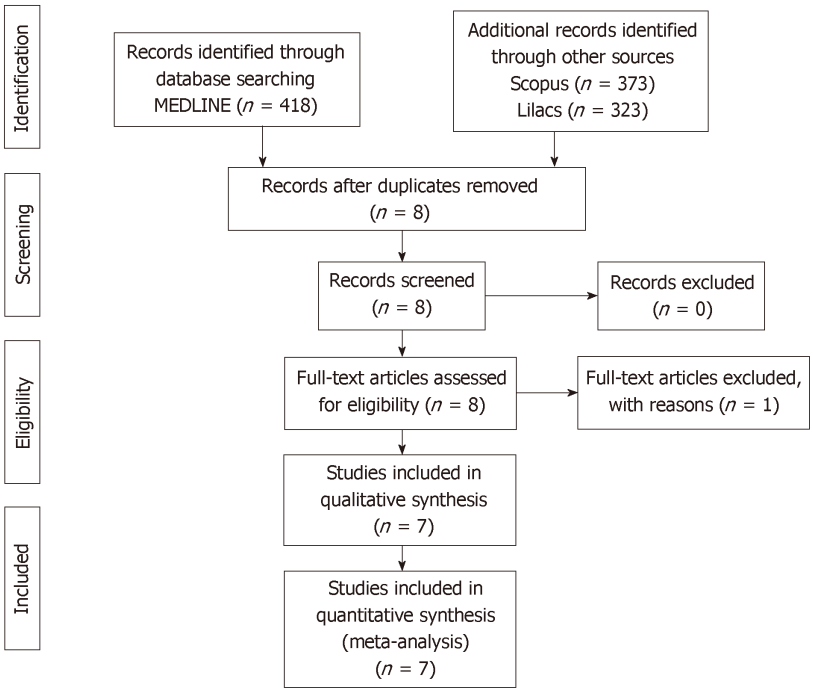

Figure 1 Research methodology based on PRISMA guidelines.

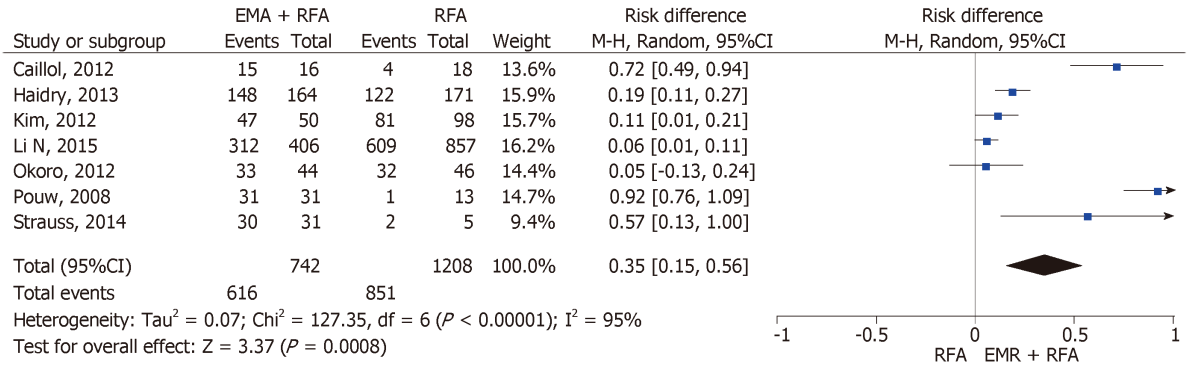

Figure 2 Comparison between the groups, in relation to the eradication of dysplasia before the sensitivity test.

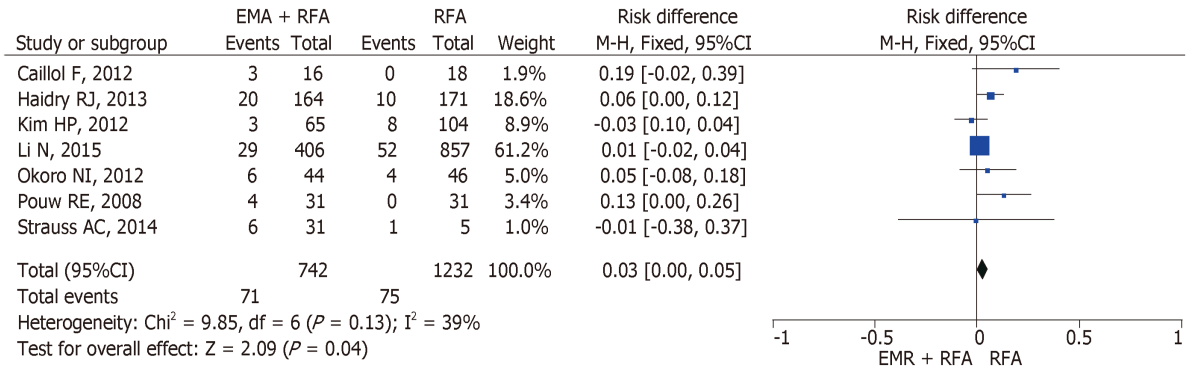

Figure 3 Comparison between the groups, in relation to stenosis.

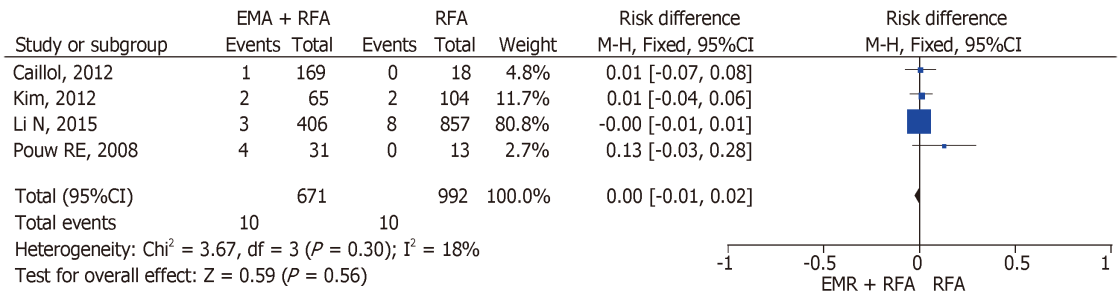

Figure 4 Comparison between the groups, in relation to bleeding.

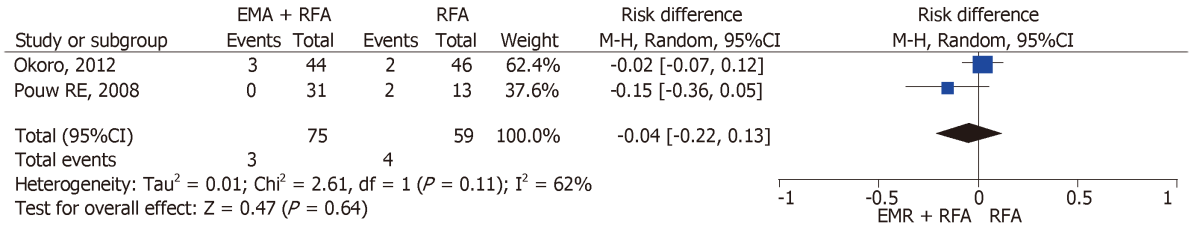

Figure 5 Comparison between the groups, in relation to chest pain.

ARTICLE HIGHLIGHTS

Research background

Barrett's esophagus (BE) remains a challenging disease. BE associated with dysplasia is a difficult diagnosis for pathologists. Additionally, the adequate treatment and close follow-up of these patients is required. With the advent of new therapies, more studies have been done to unveil the best way to treat patients with this disease. One of the most promising techniques in the management of this condition is radiofrequency ablation (RFA). This approach can also be performed combined with resection methods, such as endoscopic mucosal resection (EMR). This systematic review and meta-analysis aimed to evaluate RFA alone or combined EMR (RFA + EMR) in the treatment of high-grade dysplasia (HGD) and intramucosal carcinoma in BE.

Research motivation

Radiofrequency ablation has been recognized with the method of choice for the treatment of BE with dysplasia. However, there is a question in the literature about the need to associate resection techniques such as EMR and endoscopic submucosal dissection in the treatment of these patients. Our study aims to assess whether the association of EMR adds benefit in the treatment of BE with HGD and intramucosal carcinoma.

Research objectives

The objective of our study is to evaluate the effectiveness of RFA and RFA+EMR in patients with BE with HGD and intramucosal carcinoma. This systematic review and meta-analysis can help colleagues in decision making regarding the treatment of this condition, as well as serve as a basis for future studies related to this subject.

Research methods

This systematic review was conducted according to the PRISMA. The search was performed in electronic databases including Medline (*via* PubMed), LILACS and Cochrane. Studies comparing RFA and EMR + RFA in the treatment of HGD and intramural carcinoma were included. The Newcastle-Ottawa tool was used to evaluate the risk of bias and the applicability of primary diagnostic accuracy studies. The meta-analysis was performed using the RevMan5 software.

Research results

Seven studies were included with a total of 1950 patients, with 742 in the RFA + EMR group, and 1208 in the RFA isolate group. A higher eradication rate was observed in patients submitted to RFA + EMR compared to patients submitted to RFA isolated [RD 0.35 (0.15, 0.56)]. However, no statistical differences were observed regard to the bleeding rate, [SD 0.0 (-0.01, 0.02)], stenosis rate [RD 0.03 (0.00, 0.05)], and chest pain rate [SD -0.04 (-0.22, 0.13)].

Research conclusions

This meta-analysis corroborates the idea of performing EMR+RFA in patients with BE with HGD or intramucosal carcinoma, without increasing the number of complications associated with the combination of RFA + EMR when compared to RFA alone. We believe that the association of

these techniques allows a deeper elimination of BE with HGD or intramucosal carcinoma, without increasing the risk of the procedure for the patient, validating the association of these techniques in the treatment of this disease.

Research perspectives

This systematic review and meta-analysis can help colleagues in decision making regarding the treatment of HGD or intramucosal carcinoma in BE, as well as serve as a basis for future studies related to this subject.

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CASE REPORT

Rare sequalae of hiatal hernia causing pancreatitis and hepatitis: A case report

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Abstract

Hiatal hernia (HH) contents commonly include stomach, transverse colon, small intestine, and spleen but herniation of the pancreas is an extremely rare phenomenon.

79-year-old female with multiple comorbidities presented to emergency department with complaints of weight loss for 6 mo and abdominal pain for one day. Physical examination revealed cachectic and dehydrated female and bowel sounds could be auscultated on the right side of chest. Computed tomography of the chest and abdomen revealed interval enlargement of a massive HH, containing stomach and much of the bowel as well as pancreas and distal extra-hepatic biliary duct, probably responsible for obstructive effect upon same. There was increased prominence of the pancreas consistent with pancreatitis. There was a large HH causing obstructive effect with dilated biliary system along gall bladder wall edema and pancreatitis. Patient clinical status improved with conservative treatment.

HH presenting with acute pancreatitis is a serious diagnostic and therapeutic challenge. The initial management is conservative, even if the abdominal content has herniated to mediastinum. The incentive spirometry can be utilized in the conservative of the large HH. After stabilization of the patient, elective surgical intervention remains the mainstay of the management. Definitive treatment will vary from case to case depending on the acuity of situation and comorbidities.

Key words: Hiatal hernia; Pancreatitis; Hepatitis; Para-esophageal hernia; Gastropexy; Pancreatic herniation; Diaphragmatic hernia; Percutaneous endoscopic gastrostomy; Case report

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Core tip: Large hiatal hernia (HH) with inclusion of the pancreas in the hernial sac is extremely rare. We present a case of 79-year-old female with multiple comorbidities presented to emergency department with abdominal pain. Computed tomography of the chest and abdomen showed a large HH causing obstructive effect with dilated biliary system along gall bladder wall edema and pancreatitis. The acute pancreatitis can be from pancreatic trauma or ischemia. Transaminitis can be present from biliary traction or volvulus. As in our case, the conservative management includes incentive spirometry leading to the reduction of the hernia sac is essence of the treatment. The surgical intervention is the definitive treatment, although it varies on case to case based on the comorbidities and patient wishes.

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INTRODUCTION

Hiatal hernia (HH) is defined as protrusion of the contents of the abdomen into the thoracic cavity through the openings in the diaphragm. Ambore Pare mentioned this disease for the first time in the fifteenth century[1,2]. Most commonly stomach herniates through the diaphragm followed by other organs like transverse colon, small intestine, and spleen etc. Herniation of the pancreas through the hiatus is an extremely rare phenomena and very few cases are reported in literature which include both symptomatic and asymptomatic presentations[3,4]. Pancreatitis is the usual complication of the herniation of pancreas. Rarely, transaminitis is noted due to the traction and the extrinsic biliary obstruction in the hernia sac.

A systematic review of the literature revealed approximately 16 cases pancreatic herniation through diaphragm resulting in pancreatitis[2,5-19]. We came across three cases of transaminitis and pancreatitis due to HH and ours is the fourth case of such presentation ever reported in literature[12,17,19]. Literature search was performed using following electronic bibliographic databases: MEDLINE (Ovid SP and PubMed), Scopus and Web of Science till October of 2018. The bibliographies of retrieved articles were searched to obtain additional articles. The search terms included "hiatal hernia", "pancreatitis", "hepatitis", "transaminitis", "paraesophageal hernia", "pancreatic herniation", "diaphragmatic hernia", "Percutaneous endoscopic gastrostomy", "Gastropexy".

Here we mention a rare case of a patient diagnosed with transaminitis like due to the biliary etiology and pancreatitis due to herniation of the stomach, pancreas, gut and parts of biliary tree into the chest. Our case is novel due to rarity of the pathology and in addition, it depicts the rare association of hepatitis. We have discussed the possible pathogenesis of the acute pancreatitis and transaminitis along with its management. We have also opined on the conservative management strategies for the HH.

CASE PRESENTATION

Chief complaint

79-year-old female with presented to emergency department with one day of abdominal pain.

History of present illness

She described the pain in the right upper quadrant of abdomen as sudden onset, moderate to severe in intensity, non-radiating aching associated with chest discomfort. Patient also reported more about 8 pounds weight loss over the past 5 months and poor appetite.

History of past illness

Her medical comorbidities include Hypertension, hyperlipidemia, Gastroesophageal

reflux disease, Osteoarthritis, Rheumatoid arthritis, paraesophageal hernia. Patient denied any toxic habits.

Over the last two years' patient had the hospitalization for the abdominal pain and dizziness. She is noted to have large HH and managed for the same. She did not report the dysphagia.

Her surgical history included right breast lumpectomy for breast cancer and status post chemotherapy and radiotherapy, left eye surgery for macular degeneration and lumbar laminectomy. She denied any thoracic surgery. Family history was negative for any gastrointestinal cancers.

Physical examination

On presentation her vitals were temperature: 97.1 degrees °F, pulse of 66 bpm, respiratory rate of 19/min and blood pressure of 154/77 mmHg.

On general physical examination she looked cachectic and dehydrated. Abdominal examination revealed non-distended, soft, non-tender abdomen with no rebound tenderness and normal bowel sounds. The bowel sounds could be perceived on the right chest. Exam of the cardiovascular, pulmonary and Neurological was unremarkable. Retrospectively we were not able to corroborate the radiological finding on the physical exam.

Laboratory examinations

The hemoglobin of 13 gm/dL with interval decrease due to intravenous hydration. There is no significant leukocytosis and had thrombocytopenia. The renal function was well preserved. Patient was noted to have the elevated lipase at the time of the presentation. She had transaminitis and elevated alkaline phosphatase with the interval improvement during the hospitalization (Table 1). Her lipase was normal at the normal at the prior hospitalization before 3 mo.

Imaging examinations

During the index hospitalization she had computed tomography (CT) of the chest and abdomen with oral and intravenous contrast were for the further evaluation (Figure 1) of persistent chest discomfort. CT chest revealed interval enlargement of a massive HH, containing stomach and much of the bowel as well as pancreas and distal extrahepatic biliary duct, probably responsible for obstructive effect upon same. Increased prominence of the pancreas consistent with pancreatitis. Compressive atelectasis in portions of lung adjacent to the hernia, and mass effect upon mediastinum. CT of the abdomen and pelvis with IV contrast reported as large HH causing obstructive effect with dilated biliary system along gall bladder wall edema and pancreatitis.

Ultrasound of the abdomen showed distended gallbladder, with layering sludge, and continued visibility of intrahepatic biliary ductal dilatation; extrahepatic ducts which were seen to be dilated and massive HH.

The CT of the chest (Figure 2) performed during the prior hospitalization revealed the large HH with herniation in to chest with the stomach and colon in the its content. The pancreas was not present in the hernia content.

Final diagnosis

The final diagnosis of the presented case is Pancreatitis and hepatitis as a complication of HH.

Treatment

For the management of the acute pancreatitis patient was treated with Intravenous hydration with Lactated Ringer's Solution, analgesics along and intensive care monitoring during resuscitation. We acquired surgery consultation for large HH. In view of no signs of bowel obstruction and acute pancreatitis, no emergent or urgent intervention was recommended. The hydration therapy, monitoring the tolerance of the oral dietary intake and the incentive spirometry were the mainstay of the conservative management. The spirometry induced positive pressure is expected to reduce the HH. In view of the advanced age and the high risk from surgical complications, patient and the family perused palliative care. The interval CAT scan to review the reduction hernia content was planned but could not be done.

DISCUSSION

HH is defined as the trans-hiatal shifting of the abdominal contents into the chest which most commonly include stomach but parts of colon, small intestine, spleen, omentum can herniate along with stomach. Herniation of the pancreas is extremely

Table 1 Initial relevant laboratory values on presentation

Laboratory test	Results Before 3 mo	Result Day 1	Result Day 2	Result Day 3
Hemoglobin (g/dL) (12-16g/dL)	11.2	13.3	10.9	10.6
Hematocrit (%) (42%-51%)	34.6	39.7	33.2%	32.8 %
Leucocyte count (cells/μL) (4800-10800/μL)	6200	4600	3400	2900
Platelet count (cells/μL) (150000-400000/μL)	170000	163000	135000	117000
Blood urea nitrogen (mg/dL) (8-26 mg/dL)	12	8	8	8
Serum creatinine (mg/dL) (0.5-1.5 mg/dL)	1.2	0.8	0.6	0.4
Serum albumin (g/dL) (3.2-4.6 g/dL)	3.9	4.1	3.5	3.1
Serum total bilirubin (mg/dl) (0.2-1.1 mg/dL)	0.2	0.9	0.6	0.5
Alkaline phosphatase (unit/L) (43-160 unit/L)	68	254	207	169
Serum alanine aminotransferase (unit/L) (5-40 unit/L)	14	163	100	61
Serum aspartate transaminase (unit/L) (9-36 unit/L)	17	258	80	35
Serum lipase (unit/L) (< 61 unit/L)	38	238		

rare because pancreatic head and duodenum are retroperitoneal and fixed by ligament of treitz[20]. But stretching of the transverse mesocolon due to increase in intra-abdominal pressure causes loosening of the posterior fascia resulting in pancreatic mobilization and herniation[7].

HH is commonly observed in the western population. Women are more effected than men and the percentage of the disease increases with age. However, a recent review of literature by Jäger *et al*[3] reported 16 cases of large HH with pancreatic involvement having equal numbers of males and females men and 12 cases occurring in patients more than 60 years of age. All patients were symptomatic and diagnosed with CT imaging of the abdomen except one who was asymptomatic and diagnosed on CT chest while being investigated for intractable cough[4].

Patient with HH are usually asymptomatic but sometimes complaint of retrosternal burning, dyspepsia, epigastric and chest pain, nausea, belching, cough and shortness of breath or symptoms of mechanical cholestasis such as jaundice, itching and loose stools[3,9,16]. The exact cause is not known in most of the patients, but congenital presence of diaphragmatic weakness or large hiatus contributes to the development of HH.

The complications of HH include hematemesis associated with esophageal ulcers, esophageal erosions, anemia, gastric or intestinal obstruction and perforation. Pancreatitis and hepatitis occurring with HH are extremely rare. Pancreatitis can occur because of repetitive pancreatic trauma in the diaphragmatic hernia, or ischemia of the pancreas resulting from stretching and traction on the vascular pedicle and partial or complete obstruction of the main pancreatic duct due to abnormal folding[5,6,8,17,18]. Hepatitis can occur due to volvulus of the biliary tree and causing obstruction of the common bile duct. Therefore, etiology of the acute pancreatitis can be from the biliary cholestasis and the vascular insufficiency. It happened in our case but resolved with conservative measures. The diagnosis includes proper history and physical examination, significant elevations of serum lipase and abnormal liver function tests and imaging suggesting of pancreatic inflammation and other relevant abnormalities as mentioned above in our case. We also suggest evaluation of the vascular insufficiency and biliary causes as the etiology for acute pancreatitis in cases of HH. The reduction of the pancreas along with the hernial content is key to the management in all etiology o the acute pancreatitis.

Medical management is done for mildly symptomatic HH with gastroesophageal reflux disease. Serious symptoms of HH like chest discomfort or odynophagia due to severe esophagitis seen with paraesophageal HH require surgical intervention[21].

We suggest incentive spirometry which will be help in expansion of the lungs due to increase in intrathoracic pressure and contribute towards reduction of the herniated contents back into the abdominal cavity. This will reduce the pancreas in the abdominal cavity and cure the inciting factors for the acute pancreatitis.

The surgical modalities include reduction of the HH, repair of the defective hiatal opening, and anti-reflux surgery like fundoplication using abdominal or thoracic approaches depending on the surgeon expertise and patient wishes[21,22]. Rarely biliary stenosis occur during trans-hiatal herniation of the pancreas and duodenum resulting in cholestasis and requiring endoscopic retrograde cholangiopancreatography[3].

We present a rare clinical scenario where our patient developed pancreatitis and transaminitis during pancreatic herniation. Cases of pancreatic herniation causing

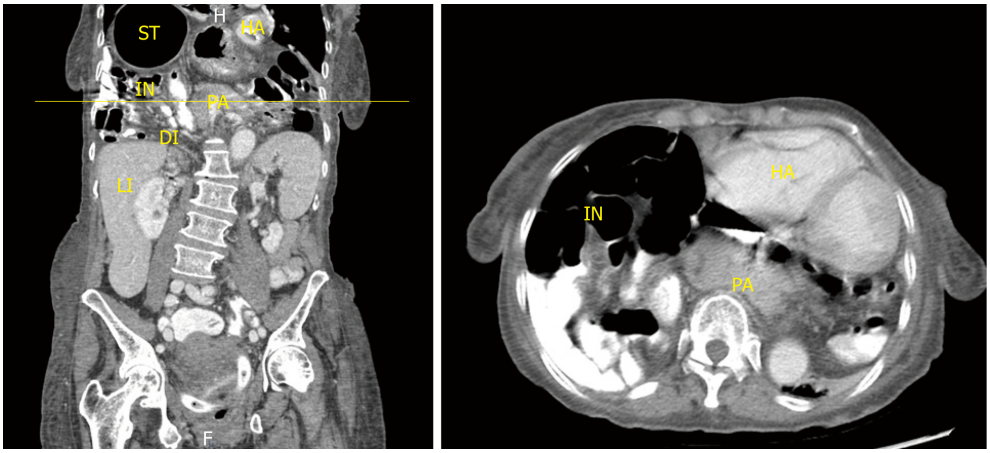

Figure 1 Demonstrate the contrast-enhanced computed tomography (oral and intravenous), coronal and axial reconstruction with large hiatal hernia with pancreas in the chest. ST: Stomach; IN: Small intestine; LI: Large intestine; PA: Pancreas; DI: Diaphragm; HA: Heart.

pancreatitis are rare and therefore ideal management is not well known[2,9]. Some cases were treated with HH surgery in the past[7] but in other cases conservative management including intravenous fluids, pain killers, diet as tolerated was done due to elevated risk of surgery or patient's refusal of treatment[2,17]. Definitive surgical treatment is required in cases of incarcerated or perforated hernias or cases refractory to medical therapy. Patient with advanced age and multiple comorbidities are also considered poor surgical candidates[21,23]. However, elective repair is needed in younger population with low surgery risk to prevent the development of further serious complications[21].

Pancreatitis in our patient was managed with fluids, analgesia, antiemetics, and gradual advancement of diet as tolerated by the patient. Our patient did not have surgery since the patient only wanted conservative treatment. Other cases are reported in literature mentioning success of the conservative management in which the patients were not the surgical candidates or refused surgical treatment[9,17,19]. In addition, gastropexy with percutaneous endoscopic gastrostomy (PEG) can be used for fixation of the stomach to the anterior abdominal wall in patients with HHs who are poor surgical candidates or refuse more risky and extensive procedures[24]. It is known that insertion of PEG tube helps in anchoring of the stomach to the anterior abdominal wall and therefore decreases the risk of volvulus[24]. We recommended same technique for patients with pancreatic HH who are unable to undergo reparative operations. This appears to be simple procedure where PEG tethers the stomach to the abdominal wall and help prevent further migration of intra-abdominal organs in the thoracic cavity[21,24]. However, symptoms of dysphagia or GERD may not improve with gastropexy[24].

Any intervention in these patients require positive pressure ventilation with or without intubation depending on the clinical status. The positive pressure may assist in reduction of the herniated contents from the thoracic cavity back into the abdominal cavity and may help worsening of the herniation during the procedure.

CONCLUSION

HH, a common clinical disease, can present rarely with acute pancreatitis. The herniated pancreas in the thoracic cavity is a serious diagnostic and therapeutic challenge. The etiology of the pancreatitis in cases of HH can be vascular or biliary in origin and should be evaluated. Whenever biliary etiology is considered likely for the acute pancreatitis, possibility of the common bile duct stricture should be considered. After stabilization of the patient, elective surgical intervention remains the mainstay of the management. If patient is not amenable to any intervention, intension spirometry should be performed to prevent lung atelectasis. Definitive treatment will vary from case to case depending on the acuity of situation and comorbidities.

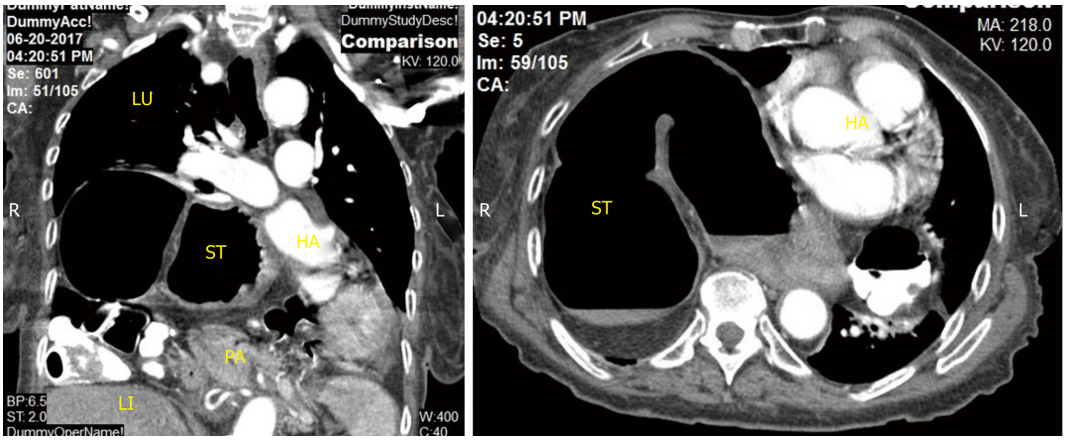

Figure 2 Demonstrate the computed tomography of the chest with large hiatal hernia. No pancreas in the hernia sac. ST: Stomach; LI: Large intestine; PA: Pancreas; HA: Heart; LU: Lung.

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CASE REPORT

Choledochoscope with stent placement for treatment of benign duodenal strictures: A case report

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Abstract

BACKGROUND

Endoscopically or fluoroscopically guided dilation is a safe and effective alternative to surgery for patients with benign strictures of the gastric outlet.

CASE SUMMARY

We describe two cases where a novel approach with a Spyglass® choledochoscope in assessing the extent of benign duodenal strictures and aiding in placement of duodenal stents for treatment of the strictures. Choledochoscope-guided wire and stent placement was successful in all cases, leading to symptom resolution related to benign duodenal obstruction. No major adverse events were observed.

CONCLUSION

Choledochoscope-guided assessment and endoscopic therapy is a viable approach in relieving duodenal obstruction, if the conventional combined fluoroscopic and endoscopic methods fail.

Key words: Choledochoscope; Duodenal stricture; Intraluminal stent; Case report

Core tip: The choledochoscope has the advantages of a smaller form factor, leading to easier passage of the scope through luminal narrowing or stricture with added benefits of

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direct visualization. Additional benefits include avoiding looping in the stomach with the passage of the choledochoscope through the therapeutic gastroscope. This study is the first to report this unique technique, with other potential applications in both benign and malignant strictures in the upper gastrointestinal tract if the conventional combined fluoroscopic and endoscopic methods fail.

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INTRODUCTION

Malignancy remains the commonest cause of gastric outlet obstruction (GOO) but benign etiologies like peptic ulcer disease and caustic ingestion are responsible for significant proportion of such patients[1]. Nonsteroidal anti-inflammatory drugs (NSAID) ingestion is an uncommon cause of GOO[2]. The principal sites of involvement in cases of obstruction are the pyloric channel and the duodenal bulb. Small bowel strictures caused by NSAIDs are short (2-3 mm) web-like and are often labeled as diaphragms[3].

Endoscopically or fluoroscopically guided dilation is a safe and effective alternative to surgery for patients with benign strictures of the gastric outlet. It is considered to be a more rapid treatment and more cost effective than surgery[4-6]. The dilation therapy coupled with anti-secretory therapy and removal of the etiology factors (*e.g.*, Helicobacter pylori) was shown to achieve long-term resolution of symptoms in 85%-100% of patient with peptic ulcer-related GOO[7]. However, the use of self-expandable metallic stents (SEMS) has been rarely reported in benign strictures[3,8,9].

The following cases highlights a novel approach in traversing duodenal strictures using a choledochoscope, combined with use of SEMS in benign duodenal strictures, in previously failed attempts with combined fluoroscopic and endoscopic guidance.

CASE PRESENTATION

Case 1

A 65 year-old man presented to the clinic with a complaint of post-prandial fullness and early satiety. The medical history of the patient was significant for peptic ulcer disease, osteoarthritis requiring NSAID, asthma, and depression. At physical exam, the abdomen was tender to palpation in the epigastric region. The vitals were normal. No pertinent laboratory or imaging was pertinent to this case.

Case 2

A 77 year-old man presented to the clinic with a complaint of postprandial nausea and vomiting. The medical history of the patient was signficant for chronic knee pain requiring NSAID use, congestive heart failure, coronary artery disease, diabetes mellitus, and sleep apnea. At physical exam, the abdomen was tender to palpation in the epigastric region. The vitals were normal. No pertinent laboratory or imaging was available.

FINAL DIAGNOSIS

Case 1

The initial esophagogastroduodenoscopy (EGD) revealed retained food in the stomach and a benign-appearing stricture at the pylorus, traversed post dilation. Another stricture involving was found in the distal bulb noted to be eccentric in location (Figure 1). The mucosa had no mucosal irregularity was smooth in appearance with cicatricle scarring and no intraluminal mass. The overall appearance was consistent with NSAID-induced stricture. No biopsies were performed. Multiple attempts at passing the balloon catheter and guidewire across the area were

unsuccessful despite using fluoroscopic guidance (Figure 2).

Case 2

The initial EGD revealed a two serial stricture around the C-sweep of the duodenum, which could not be traversed with a diagnostic gastroscope or ultrathin endoscope. The mucosa had no mucosal irregularity was smooth in appearance with cicatricle scarring and no intraluminal mass. The overall appearance was consistent with NSAID-induced stricture. No biopsies were performed. A guidewire was advanced across the first stricture but could not be advance pass the second stricture. Balloon dilation was attempted using a controlled radial expansion (CRE) balloon but given the short distance between the two strictures, the balloon was inadequately positioned across the stricture.

TREATMENT

Case 1

The repeat procedure was performed using a therapeutic gastroscope, allowing the passage of a Spyglass® choledochoscope (10 Fr outer diameter, 230 cm in length) with direct visualization of the lumen of the stricture (Figure 3 and 4). Then a guidewire was advanced through the choledochoscope (Figure 5), with subsequent stenting of the stricture (Figure 6 and 7) using an uncovered SEMS (WallFlex™ Duodenal Stent 22 mm by 90 mm), which was removed in 10 d. The stricture extension involvement was post bulbar which raised the issue of ampullary obstruction with covered stenting. Self-expanding stents utilized for the procedure were thus uncovered to avoid ampullary obstruction. Serial dilation was performed, using wire-guided CRE balloon over three sessions every 2 wk, with the final dilation performed to 20 mm.

Case 2

The repeat procedure was performed using a therapeutic gastroscope, allowing the passage of a Spyglass® choledochoscope with direct visualization of the lumen of the two strictures. A guidewire was advanced through the choledochoscope, followed by dilation (12 mm) and subsequent stent placement (WallFlex™ Duodenal Stent 22 mm by 90 mm) crossing both strictures, which was removed in 10 d.

OUTCOME AND FOLLOW-UP

The patients were both appropriately counseled on avoidance of NSAID and continued to adhere to the recommendation throughout the treatment. Following the initial stent placement, both patients progressed from liquid to soft diet. They progressed to solid diet following the conclusion of the aforementioned procedures, without complications. Both patients progressed from liquid to soft diet without complications.

DISCUSSION

In this study we described a novel approach for traversing duodenal stricture using a choledochoscope. Both cases of duodenal strictures initially could not be traversed using the conventional combined fluoroscopic and endoscopic methods. Direct visualization of the stricture with a passage of the choledochoscope aided in traversing the narrowed lumen and subsequent intervention using a SEMS for the treatment of the duodenal obstruction.

Endoscopically or fluoroscopically guided dilation has proven to be an effective alternative to surgery for patients with benign duodenal strictures. The use of SEMS is an established palliative treatment to relieve the obstructive symptoms of inoperable gastrointestinal tract malignancy with stenotic change. The SEMS application in benign duodenal obstruction however has been rarely reported. All the previous studies have small sample size and it was concluded that stenting for benign duodenal obstruction is an effective treatment modality[8,9]. It is postulated that better symptom management could be obtained by gradual and continuous dilatation with SEMS in the stenotic segment. The results show that there are low rates of recurrences after stenting and it reduces the need for further invasive procedures. The most common complications of the stent placement included stent migration and stent ingrowth. Neither complications were seen in our cases.

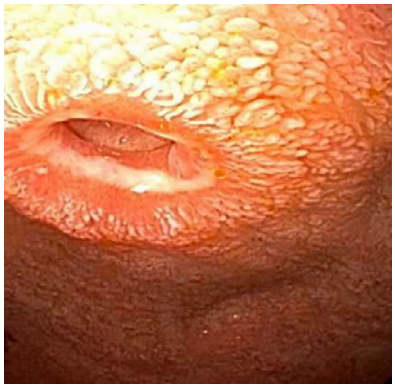

Figure 1 Endoscopic view of the duodenal bulb with the stricture.

CONCLUSION

The choledochoscope has the advantages of a smaller form factor, leading to easier passage of the scope through the stenosis with added benefits of direct visualization. Additional benefits include avoiding looping in the stomach (*e.g.*, ultrathin gastroscope) with the passage of the scope through the therapeutic gastroscope. This study is the first to report this unique technique, with other potential applications in both benign and malignant strictures in the upper gastrointestinal tract if the conventional combined fluoroscopic and endoscopic methods fail.

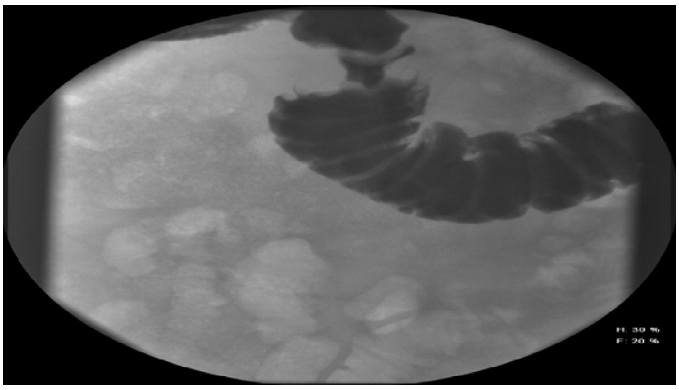

Figure 2 Upper gastrointestinal series revealing the extent of the duodenal stricture.

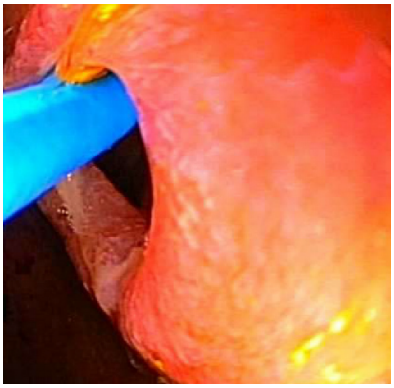

Figure 3 Endoscopic view showing the choledochoscope advanced out from the therapeutic gastroscope traverse across the stricture.

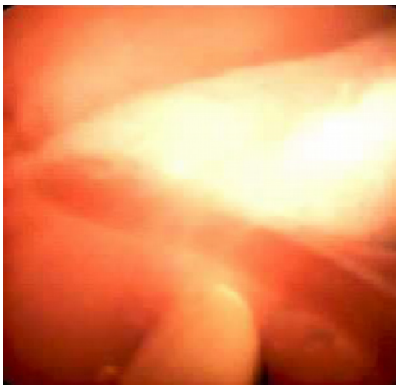

Figure 4 Endoscopic view from the choledochoscope with direct visualization of the stenosis.

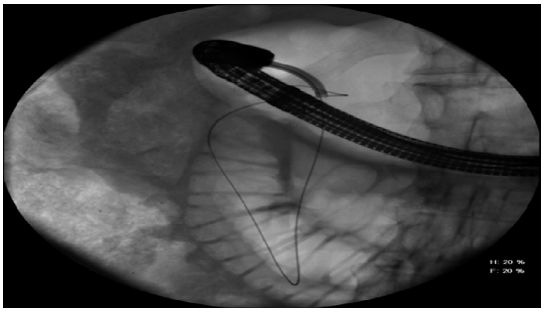

Figure 5 Radiographic view of the choledochoscope (advanced through the therapeutic gastroscope) crossing the duodenal stenosis and allowing passage of the guidewire.

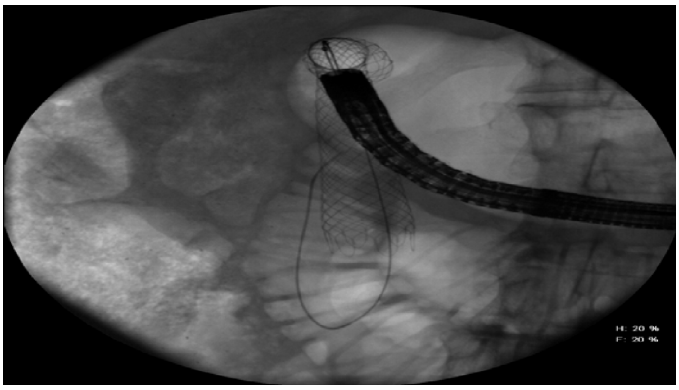

Figure 6 Radiographic view of the guidewire-directed stent placement crossing the duodenal stenosis.

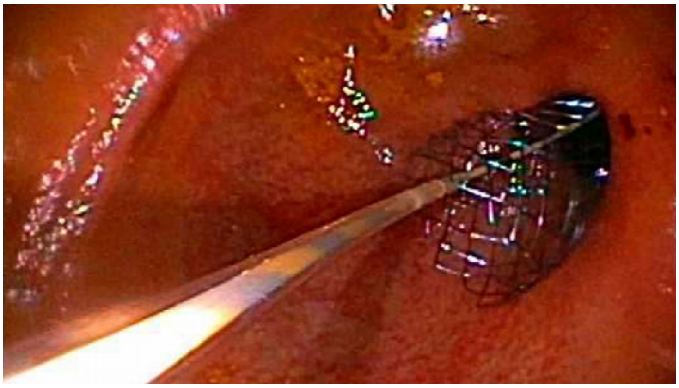

Figure 7 Endoscopic view of the stent deployment.

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