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EDITORIAL

Laparoscopic liver resection: Toward a truly minimally invasive approach

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Abstract

In the surgical treatment of hepatocellular carcinoma and colorectal liver metastasis, it is important to preserve sufficient liver volume after resection in order to avoid post-hepatectomy liver sufficiency and to increase the feasibility of repeated hepatectomy in case of intrahepatic recurrence. Parenchyma-sparing approach, which minimizes the extent of resection while obtaining sufficient surgical margins, has been developed in open hepatectomy. Although this approach can possibly have positive impacts on morbidity and mortality, it is not popular in laparoscopic approach because parenchyma-sparing resection is technically demanding especially by laparoscopy due to its intricate curved transection planes. "Small incision, big resection" is the words to caution laparoscopic surgeons against an easygoing trend to seek for a superficial minimal-invasiveness rather than substantial patient-benefits. Minimal parenchyma excision is often more important than minimal incision. Recently, several reports have shown that technical evolution and accumulation of experience allow surgeons to overcome the hurdle in laparoscopic parenchyma-sparing resection of difficult-to-access liver lesions in posterosuperior segments, paracaval portion, and central liver. Laparoscopic surgeons should now seek for the possibility of laparoscopic parenchyma-sparing hepatectomy as open approach can, which we believe is beneficial for patients rather than just a small incision and lead laparoscopic hepatectomy toward a truly minimally-invasive approach.

Key words: Laparoscopy; Liver resection; Hepatectomy; Minimally-invasive; Parenchyma-sparing; Laparoscopic surgery; Hepatocellular carcinoma; Liver metastasis; Liver lesion; Colorectal carcinoma

Core tip: In the surgical treatment of hepatocellular carcinoma and colorectal liver metastasis, it is important to preserve sufficient liver volume after resection in order to avoid post-hepatectomy liver sufficiency and to increase the feasibility of repeated hepatectomy in case of intrahepatic recurrence. Parenchyma-sparing hepatectomy has been developed for the best remnant liver function as well as sufficient surgical margins and

may have positive impacts on morbidity and mortality. Surgeons should overcome the technical difficulty and seek for the possibility of laparoscopic parenchyma-sparing hepatectomy, which will lead laparoscopic hepatectomy toward a truly minimally-invasive and beneficial approach.

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TOWARD A TRULY MINIMALLY-INVASIVE LIVER RESECTION

I remember the words, "small incision, big resection", in the keynote lecture by Professor Henri Bismuth at the European Association for Endoscopic Surgery meeting in 2011, which cautioned laparoscopic surgeons against an easygoing trend to seek for a superficial minimal-invasiveness of hepatectomy rather than substantial patient-benefits.

Laparoscopic hepatectomy has become popular[1-4] and is the standard of care[3] to treat lesions in the left lateral section[5] or peripheral anteroinferior segments[6,7] with better short-term outcomes compared to open hepatectomy, including less blood loss, less pain, and earlier recovery[8,9]. In addition, increasing number of laparoscopic major hepatectomy is actively performed in specialized centers all over the world[2,10], based on the recognition that such benefits may confirm the superiority of laparoscopic hepatectomy as a minimally-invasive surgical treatment compared to open hepatectomy. However, now is the time to reconsider if laparoscopy is truly minimally-invasive and advantageous for patients. Hepatectomy is different from other visceral surgery with regard to the importance of postoperative remnant organ function. Post-hepatectomy liver sufficiency is a life-threatening complication, mainly observed in hepatocellular carcinoma (HCC) patients with cirrhosis or colorectal metastases (CLM) patients after prolonged chemotherapy. Even after successful hepatectomy, both HCC and CLM patients may develop intrahepatic recurrence and then the possibility of repeated hepatectomy depends on the liver functional reserve. As Professor Bismuth cautioned, "big resection with small incision" should not be beneficial for patients compared to "small resection with big incision".

In seeking for both sufficient surgical margins and the best remnant liver function, parenchyma-sparing hepatectomy, including mono-segmentectomy[11] and combination of minor resections[12], has been developed in open hepatectomy. On the other hand, parenchyma-sparing approach is not popular in laparoscopic hepatectomy. This is because laparoscopy has a significant limitation of forceps manipulation so that making intricate curved transection planes for parenchyma-sparing hepatectomy is much more demanding in laparoscopic approach than in open approach. In our opinion, major hepatectomy with a single and straight transection plane, such as right and left hepatectomy, is easier and more suitable for laparoscopy, compared to anatomical or non-anatomical minor resection. For this reason, large resection, which excises non-tumorous parenchyma more than required to obtain sufficient surgical margins, is often performed by laparoscopy for small-to-intermediate-sized lesions in difficult-to-access areas. Recently, several reports have shown that technical evolution and accumulation of experience allow surgeons to overcome the hurdle in laparoscopic parenchyma-sparing resection of difficult-to-access liver lesions[13] in posterosuperior segments[14,15], paracaval portion[16], and central liver[17]. We believe laparoscopic surgeons should now reconsider the importance of parenchyma-sparing hepatectomy and try to minimize the extent of resection by laparoscopy as open approach can. "Small incision, minimum resection required for oncologic principles" should lead laparoscopic hepatectomy toward a truly minimally-invasive and beneficial approach.

REFERENCES

1 **Buell JF**, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D'Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espat J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttil R, Belghiti J, Strasberg S, Chari RS. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009; **250**: 825-830 [PMID: 19916210 DOI: 10.1097/SLA.0b013e3181b3b2d8]

2 **Dagher I**, Gayet B, Tzanis D, Tranchart H, Fuks D, Soubrane O, Han HS, Kim KH, Cherqui D, O'Rourke N, Troisi RI, Aldrighetti L, Bjorn E, Abu Hilal M, Belli G, Kaneko H, Jarnagin WR, Lin C, Pekolj J, Buell JF, Wakabayashi G. International experience for laparoscopic major liver resection. *J Hepatobiliary Pancreat Sci* 2014; **21**: 732-736 [PMID: 25098667 DOI: 10.1002/jhbp.140]

3 **Hibi T**, Cherqui D, Geller DA, Itano O, Kitagawa Y, Wakabayashi G. International Survey on Technical Aspects of Laparoscopic Liver Resection: a web-based study on the global diffusion of laparoscopic liver surgery prior to the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan. *J Hepatobiliary Pancreat Sci* 2014; **21**: 737-744 [PMID: 25088825 DOI: 10.1002/jhbp.141]

4 **Nguyen KT**, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250**: 831-841 [PMID: 19801936 DOI: 10.1097/SLA.0b013e3181b0c4df]

5 **Chang S**, Laurent A, Tayar C, Karoui M, Cherqui D. Laparoscopy as a routine approach for left lateral sectionectomy. *Br J Surg* 2007; **94**: 58-63 [PMID: 17054316 DOI: 10.1002/bjs.5562]

6 **Cho JY**, Han HS, Yoon YS, Shin SH. Experiences of laparoscopic liver resection including lesions in the posterosuperior segments of the liver. *Surg Endosc* 2008; **22**: 2344-2349 [PMID: 18528623 DOI: 10.1007/s00464-008-9966-0]

7 **Cho JY**, Han HS, Yoon YS, Shin SH. Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. *Surgery* 2008; **144**: 32-38 [PMID: 18571582 DOI: 10.1016/j.surg.2008.03.020]

8 **Yin Z**, Fan X, Ye H, Yin D, Wang J. Short- and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. *Ann Surg Oncol* 2013; **20**: 1203-1215 [PMID: 23099728 DOI: 10.1245/s10434-012-2705-8]

9 **Schiffman SC**, Kim KH, Tsung A, Marsh JW, Geller DA. Laparoscopic versus open liver resection for metastatic colorectal cancer: A metaanalysis of 610 patients. *Surgery* 2015; **157**: 211-222 [PMID: 25282529 DOI: 10.1016/j.surg.2014.08.036]

10 **Nomi T**, Fuks D, Kawaguchi Y, Mal F, Nakajima Y, Gayet B. Laparoscopic major hepatectomy for colorectal liver metastases in elderly patients: a single-center, case-matched study. *Surg Endosc* 2014; Epub ahead of print [PMID: 25149638 DOI: 10.1007/s00464-014-3806-1]

11 **Makuuchi M**, Hashikura Y, Kawasaki S, Tan D, Kosuge T, Takayama T. Personal experience of right anterior segmentectomy (segments V and VIII) for hepatic malignancies. *Surgery* 1993; **114**: 52-58 [PMID: 8356527]

12 **Torzilli G**, Procopio F, Botea F, Marconi M, Del Fabbro D, Donadon M, Palmisano A, Spinelli A, Montorsi M. One-stage ultrasonographically guided hepatectomy for multiple bilobar colorectal metastases: a feasible and effective alternative to the 2-stage approach. *Surgery* 2009; **146**: 60-71 [PMID: 19541011 DOI: 10.1016/j.surg.2009.02.017]

13 **Ishizawa T**, Gumbs AA, Kokudo N, Gayet B. Laparoscopic segmentectomy of the liver: from segment I to VIII. *Ann Surg* 2012; **256**: 959-964 [PMID: 22968066 DOI: 10.1097/SLA.0b013e31825ffed3]

14 **Gumbs AA**, Gayet B. Video: the lateral laparoscopic approach to lesions in the posterior segments. *J Gastrointest Surg* 2008; **12**: 1154 [PMID: 18193325 DOI: 10.1007/s11605-007-0455-x]

15 **Ogiso S**, Conrad C, Araki K, Nomi T, Anil Z, Gayet B. Laparoscopic Transabdominal with Transdiaphragmatic Access Improves Resection of Difficult Posterosuperior Liver Lesions. *Ann Surg* 2014; In press

16 **Yoon YS**, Han HS, Cho JY, Kim JH, Kwon Y. Laparoscopic liver resection for centrally located tumors close to the hilum, major hepatic veins, or inferior vena cava. *Surgery* 2013; **153**: 502-509 [PMID: 23257080 DOI: 10.1016/j.surg.2012.10.004]

17 **Conrad C**, Ogiso S, Inoue Y, Shivathirthan N, Gayet B. Laparoscopic parenchymal-sparing liver resection of lesions in the central segments: feasible, safe, and effective. *Surg Endosc* 2014; Epub ahead of print [PMID: 25391984 DOI: 10.1007/s00464-014-3924-9]

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REVIEW

Intentional ingestions of foreign objects among prisoners: A review

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Abstract

The intentional ingestion of foreign objects (IIFO) is described more commonly in prison populations than in the general population, with an estimated annual incidence of 1 in 1900 inmates in our state correctional facilities. Incidents often involve ingestion of small metal objects (*e.g.*, paperclips, razor blades) or other commonly available items like pens or eating utensils. Despite ingestion of relatively sharp objects, most episodes can be clinically managed with either observation or endoscopy. Surgery should be reserved for those with signs or symptoms of gastrointestinal perforation or obstruction. For those with a history of IIFO, efforts should focus on prevention of recurrence as subsequent episodes are associated with higher morbidity, significant healthcare and security costs. The pattern of IIFO is often repetitive, with escalation both in frequency of ingestions and in number of items ingested. Little is known about successful prevention strategies, but efforts to monitor patients and provide psychiatric care are potential best-practice strategies. This article aims to provide state-of-the art review on the topic, followed by a set of basic recommendations.

Key words: Ingestion; Foreign body; Endoscopy; Prisoner; Swallower; Prevention; Recurrence

Core tip: Intentional ingestion of foreign objects typically involves ingestion of small objects (*e.g.*, paperclips, razor blades, pens, eating utensils). Most episodes can be managed with either observation or endoscopy. Surgery should be reserved for those with signs or symptoms of gastrointestinal perforation or obstruction. Due to the documented pattern of escalation, efforts should focus on prevention of recurrence as subsequent episodes are associated with higher morbidity, and significant healthcare and security costs. There are no proven prevention strategies, but efforts to closely monitor patients and provide early psychiatric intervention are among recommended best-practice strategies.

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INTRODUCTION

Intentional ingestion of foreign objects (IIFO) is a

serious problem that chronically affects the United States prison population. Although other non-prisoner patients, specifically those with severe psychiatric conditions, have been reported to have the propensity toward IIFO, the prison population seems unique in that the magnitude of the problem is especially high[1-3]. It has been estimated that up to 1500 deaths may be attributable to IIFO annually in the United States alone[4]. IIFO is a seemingly preventable phenomenon that is associated with high costs of care as well as security costs for transporting and guarding inmates while hospitalized[5]. Health care costs associated with IIFO accounted for $6.5 billion of the $36.8 billion spent to manage the correctional system budgets of 44 states[6]. In a recent study, IIFO episodes were associated with healthcare-related median charges between $4683 and $7698 for those evaluated in the emergency department and admitted[5]. Male sex, incarceration, and psychiatric disease are the predominant factors associated with IIFO[7].

The management of IIFO was revolutionized by the widespread adoption of endoscopic techniques that can be used for retrieval of accessible ingested objects[8]. The prisoner population presents unique challenges due to the multifactorial interaction of psychiatric disease, the (less likely) potential for secondary gain, and the escalating nature of recurrent IIFO. Inmates treated for IIFO often return after variable time intervals having ingested larger, more dangerous, or more toxic objects[2]. These extenuating factors should prompt careful consideration of treatment options as overly aggressive treatment can often lead to disastrous complications.

LITERATURE SEARCH

An exhaustive literature search was performed using the terms "foreign body ingestion", "foreign object ingestion", "intentional ingestion", "swallowed object", and "ingestion". We utilized the United States National Library of Medicine NIH PubMed service, as well as Google™ Scholar to identify as many pertinent English literature sources as possible. After narrowing down the publication list to case reports, case series, reviews, retrospective and prospective studies, the search was further focused on epidemiology, diagnosis, management, and prevention as additional search terms. Results were tabulated, with all major studies on the topic published to date and compiled into a comprehensive, definitive list (Table 1).

EPIDEMIOLOGY

The epidemiology of intentional foreign object ingestions continues to be poorly understood. Most literature focusing on foreign object ingestions is in the pediatric literature, where the size of the gastrointestinal (GI) tract is smaller and many objects become lodged in the pharynx or esophagus posing an aspiration, toxicity, or erosion risk[9-11]. Psychiatric and prison populations account for the majority of adults presenting with foreign object ingestions, the vast majority of which were non-accidental[2]. Due to the unique characteristics of these populations, relatively few of these patients tend to present to community hospitals. In the United States these patients are typically cared for in "safety net" hospitals, making IIFO a relatively high-frequency occurrence in select hospitals. While a general IIFO incidence in the community is not known, the annual incidence of IIFO requiring evaluation in the emergency room or hospital from 2006-2010 in the prison population in the State of Ohio was 0.0528% or approximately 1 in 1900 inmates, making the disease quite rare in this high risk population (see Table 1). Unfortunately in the prison population, recurrent ingestions are also relatively more common[2,5]. The epidemiology of recurrent IIFO is less well understood. Grimes *et al*[7] found no evidence that conscious sedation, esophageal pathology, or age had any statistical significance as a significant predictor of recurrent ingestion. Repeat ingestors are more likely to ingest foreign objects and less likely to experience food impaction[7]. Impulsivity, secondary gain, or an undiagnosed psychiatric disorder are possible explanations for ingestions in the prison population[7].

Table 1 Incidence of Ingestions 2006-2010 in the Ohio Department of Rehabilitation and Corrections

Year	IIFO incidents seen (*n*)	Total prisoners incarcerated[12] (*n*)
2006	17	48534
2007	20	49691
2008	22	50371
2009	47	50371
2010	26	50944
	132	249911 (5-yr census)

Several case series and observational studies of IIFO in adults have been published[1-4,7,8,13-20]. Many of these studies included prisoners, but some included a mix of general psychiatric patients as well. Table 2 summarizes the world published literature on adult IIFO. While children commonly ingest toys, coins, and loose household items, inmates and psychiatric patients are much more likely to ingest sharp and relatively dangerous objects such as blades, improvised shanks, and metal hardware and instruments. Table 3 reviews the types of objects frequently ingested in the published literature.

HEALTHCARE COSTS

The costs of IIFO in the inmate population are high, especially when compared to the non-incarcerated population[21]. It has been estimated that the overall cumulative annual costs of IIFO in the majority (44 out of 50) United States states exceed $6 billion[6].

Table 2 Published series of intentional ingestion of foreign objects with patient treatment plans when available *n* (%)

Ref.	Year	Patients (*n*)	Not undergoing intervention	With psych dx	Surgery	Endoscopy	Objects ingested (*n*)
O'Sullivan *et al*[1]	1996	36 (20 prisoners)	31 (86)	6 (16)	2 (6)	4 (11)	308
[1]Dalal *et al*[2]	2013	30 (141 episodes)	33 (23)	27 (19)	11 (7)	97 (68)	649
[1]Weiland *et al*[3]	2002	22 (256 episodes)	23 (9)		10 (4)	64 (25)	256
Barros *et al*[4]	1991	167 (39 prisoners)	14 (8)	6 (3)	51 (30)	117 (70)	167
Selivanov *et al*[8]	1984	100	42 (42)	4 (6)	12 (12)	42 (42)	101
Blaho *et al*[13]	1998	8	8 (100)	6 (75)			14
Velitchkov *et al*[14]	1996	542 (379 prisoners)	410 (75)	124 (23)	26 (5)	19 (3)	1203
Karp *et al*[15]	1991	19		18 (95)			
[1]Lee *et al*[17]	2007	33 (52 episodes)	0		6 (12)	46 (88)	104
Bisharat *et al*[18]	2008	11	7 (63)		3 (27)	2 (18)	
Huang *et al*[19]	2010	33	4 (12)	27 (81)	2 (6)	299	305
Ribas *et al*[20]	2014	82	142	62 (75)	5 (6)	15 (18)	162
Grimes *et al*[7]	2013	159 (23 prisoners)		34 (21)	5 (3)	231	254
Total		2613	1014 (39)	317 (12)	190 (7)	1129 (43)	3153

[1]Many presented with multiple episodes. Not all studies reported all data. Some studies may include some non-intentional ingestions.

Table 3 Most common types of objects ingested

O'Sullivan *et al*[1]	Batteries, sharp metal objects (nails, razor blades, pins)
Dalal *et al*[2]	Pens, razor blades, spoons, sporks[1], toothbrush, screws, bolts
Weiland *et al*[3]	Metal bezoars
Barros *et al*[4]	Wires, needles, balloons (filled with narcotics)
Selivanov *et al*[8]	Coins, bones, food, razor blades, safety pins
Blaho *et al*[13]	Razor blades
Velitchkov *et al*[14]	Screws, pins, spoons
Huang *et al*[19]	Pens, batteries, knives
Karp *et al*[15]	Razors, glass, toothbrush
Lee *et al*[17]	Metal wires, pens, toothbrush, needles
Bisharat *et al*[18]	Razors, batteries
Ribas *et al*[20]	Razor blades, cylindrical batteries, mattress springs
Grimes *et al*[7]	Toothbrush, pencil

[1]Spork: Functional combination of a spoon and a fork.

The majority of IIFO care costs can be broken down into nursing care (56%), endoscopy services (14%), emergency department care (10%), and surgical services (6%)[19]. Considering the above, IIFO episodes were associated with healthcare-related median charges between $4683 and $7698 for both emergency department evaluations and hospital admissions[5]. In the subset of patients who required hospital admission, median per-episode charges exceeded $14000[5]. Moreover, when repeated episodes of IIFO are factored in, estimated cumulative "lifetime" charges for patients studied in the same cohort were nearly $50000[5]. In addition there are the costs of security and transportation to the prison system because these patients have to be transported in a secure fashion, typically with multiple guards. While hospitalized, a guard must remain at the patient bedside. Hospitals also cover the cost of around-the-clock security for non-prisoner psychiatric patients. The estimated cost not reimbursed by third party payers for security was $278806 in Rhode Island over an eight year span[19].

DIAGNOSIS (VERIFICATION)

Actual ingestions

Most ingestions are either self-reported by the inmate or witnessed by security staff. Patients presenting typically receive a plain X-ray to localize the object. Patients with normal vital signs and normal physical exam typically do not require additional imaging, even in the setting of sharp or other seemingly more dangerous objects.

Plain abdominal X-ray demonstrating free air is considered diagnostic for perforation. However, free air under the diaphragm is rarely seen because perforations are most commonly caused by impactions that have slowly eroded through the intestinal wall. These erosions are covered by fibrin, omentum, or adjacent loops of bowel limiting the passage of free air into the peritoneal cavity[22].

Patients with abdominal pain, fever, gastrointestinal bleeding, or other symptoms typically require CT scanning to evaluate for the presence of bowel perforation or other pathology. It has been shown that prisoners sometimes choose objects that will be visible on radiographs, wrap them in plastic or other materials to reduce the risk of injury, and then feign gastrointestinal symptoms[20]. Most objects are located in the stomach at the time of initial presentation (Figure 1). After initial X-ray, no additional workup is typically performed for radiolucent objects unless mandated by abnormal physical exam findings or vital signs.

Fictitious ingestions

Claimed or fictitious ingestions have been reported[13]. Although speculative, there are three possible explanations for this observed pattern: (1) some form of secondary gain may be present when an ingestion is claimed; (2) an actual ingestion may have occurred but the object ingested is not readily detectable or has already passed through the gastrointestinal system; or (3) the patient may be contemplating ingestion, but has

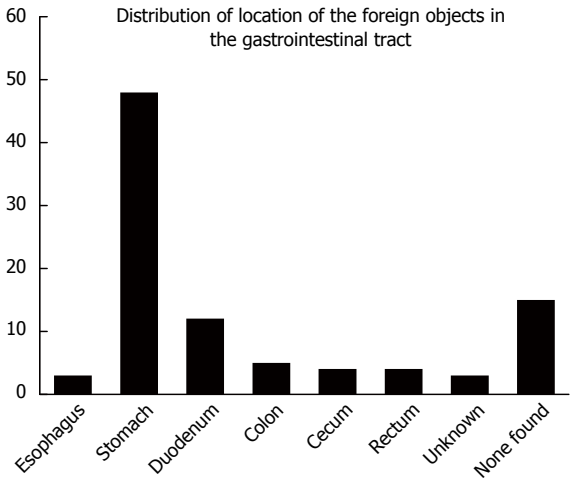

Figure 1 Distribution of intentional ingestion of foreign objects in the gastrointestinal tract in inmate. (From Dalal *et al*[2] Figure 2, permission pending).

not yet committed to this self-destructive behavioral pattern. It is important to note that healthcare-related median charges associated with verified (*i.e.*, proven) ingestions are higher ($5860) than charges associated with claimed (*i.e.*, fictitious) ingestions ($3997)[5].

MANAGEMENT

General principles

Like any surgical emergency, initial management is typically based on physical examination and patient physiology. Patients with peritonitis typically require immediate surgical exploration[2]. Selective endoscopy is appropriate for many intragastric objects and can prevent progressive peristalsis of the object (with its associated dangers)[2,4,8]. In inmate and psychiatric populations surgical exploration should be avoided when possible as the benefits of operative removal often do not outweigh the risks of surgery. Drug and contraband smuggling, known as "body packing," is another event that should be recognized. Ribas *et al*[20] reported on 36 patients attempting to smuggle cocaine by ingesting packets containing the drug. These "body packers" usually do not undergo endoscopy for fear of rupture and surgery is usually only performed if the patient develops symptoms. The operative course itself may be difficult due to the adhesions of previous laparotomies, often due to prior such incidents, and patients with the associated psychiatric comorbidities may have a difficult postoperative course.

In our practice there is a high rate of wound complications, self-inflicted wound mutilation (including self-inflicted evisceration of the midline laparotomy site), and non-compliance with physician orders (such as violation of nothing-by-mouth orders resulting in aspiration of gastric contents). Prisoners who develop complications of surgery for IIFO are at risk for the development of intestinal fistula and we have observed generally poor outcomes of both operative and non-operative management of fistulas in this population, with high rates of readmission, parenteral nutrition-associated line infections, abdominal wall infections, and non-healing wounds. In our previous work we reported the various management strategies employed for 141 episodes of IIFO in inmates (Table 4)[2].

Table 4 Relative frequency of intentional ingestion of foreign objects management strategies employed in 141 episodes of intentional ingestion of foreign objects

No intervention	16%
Hospital admission	10%
Surgery alone	5%
Endoscopy + surgery	3%
Endoscopy alone	12%
Endoscopy (successful)	54%

Observation

In the vast majority of cases (approximately 67%-80%) expectant management will suffice, including watchful waiting and serial physical exams, with or without concurrent radiographic assessments[1,8,14]. Most of the foreign bodies that clear the stomach will spontaneously pass through the gastrointestinal system, frequently within a week[3,8]. Fortunately, many of the IIFO episodes end up being self-limited, and do not require formal hospital admission[22]. The need for admission is present in 7%-33% of patients[1,13]. In one series of 141 ingestions, the risk of hospital admission was independently associated with elevated white blood cell count [odds ratio (OR) 1.4] and increasing number of items ingested (OR 1.3)[2].

Endoscopy

Endoscopy has revolutionized the management of IIFO. In fact, the forward-viewing flexible endoscope is the first option for retrieval of foreign objects in the stomach and duodenum[23]. Most ingested objects can be retrieved endoscopically, as long as they have not progressed beyond the ligament of Treitz. Successful endoscopic retrieval of IIFO has been reported in 19.5%-53.9% of cases[2,14]. Some of the more common objects retrieved by endoscopy are coins, bones, and impacted food[8]. In one study, the successful performance of endoscopy with retrieval of the IIFO has been found to reduce the risk of surgery by over 85%[2]. Having said that, endoscopy has also been associated with high failure rates and complications by others, thus warranting careful consideration when implementing this therapeutic option[3]. Grimes *et al*[7] found first time ingestors were more likely to have a food impaction compared to recurrent ingestors who were more likely to have ingested metal objects; however, recurrent ingestors experienced food impactions as well, commonly due to esophageal stricture[7]. In the same study one patient was found to be responsible for 67 ingestions (22%)

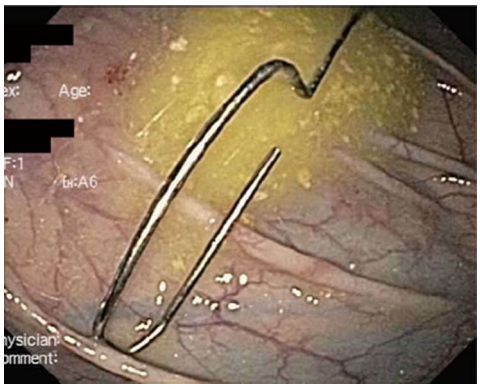

Figure 2 Paperclip in the ascending colon noted on colonoscopy (image rights belong to the authors).

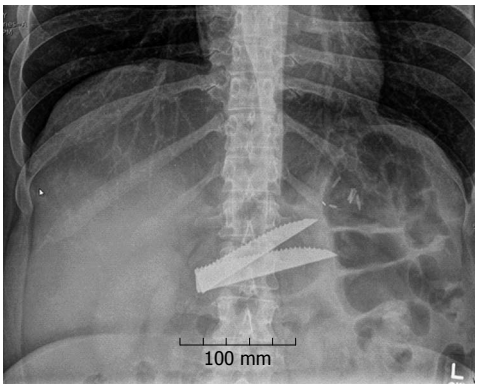

Figure 3 Steak knife blades in the stomach (image rights belong to the authors).

of the ingestions. On average there were 9.2 episodes per patient. They also found that endoscopy was more successful in single ingestion patients, supporting the idea that the more times a patient ingests an object the more complex the ingestion becomes. Most objects that pass the ligament of Treitz are likely to pass through the entire GI tract. Rarely, small objects can become impacted in the colon. Endoscopy is frequently successful in removing those small objects such as the paperclip that was removed by the author (D.C.E.) depicted in Figure 2. While some sharp objects such as small razor blades can be removed endoscopically, particularly with the use of hoods, available endoscopic equipment and local practices may vary and we cannot draw any conclusions regarding recommendations for specific strategies for objects of various shapes, sizes, or sharpness.

Surgery

Operative intervention is required in up to 30% of IIFO cases[1,2,4,8,14], although more recent series report lower rates (*i.e.*, < 15%) of operative intervention in this population[1,2]. In one large retrospective study, factors independently associated with risk of surgery in the setting of IIFO included elevated white blood cell count (OR 1.6) and increasing number of ingested items (OR 1.1 per item)[2]. Not surprisingly, failure of endoscopy has been associated with the need for subsequent operative intervention[4]. It has been noted that thinner, sharper foreign objects mandate a higher index of clinical suspicion due to higher perforation risk[14]. Also, surgery may be more likely in cases of proximally located IIFO, especially when the object is > 6-7 cm in largest dimension[14]. Previous surgery, obstruction, and narrowing all predispose to impaction of an object and increase the possible need for surgical intervention[22]. Long objects, such as the intragastric steak knife blades shown on abdominal X-ray (Figure 3), frequently require laparotomy. The author (D.C.E.) retrieved one blade endoscopically but the other became impacted at the esophageal hiatus and required laparotomy with gastrotomy for removal.

Figure 4 Balls of narcotics wrapped in plastic wrap. These required surgical removal in a prisoner who was engaged smuggling activities by "body packing" (image rights belong to the authors).

IIFO impaction is also possible, particularly in the ileo-cecal area[14]. The ileocecal region is particularly prone to obstruction by objects less than 6 cm that are able to maneuver through the duodenum[22]. Velitchkov *et al*[14] advocate an appendicostomy approach to retrieval of IIFO impacted in this location, however, most surgeons would prefer a simple enterotomy with foreign object retrieval, followed by repair of the enterotomy[14]. Figure 4 depicts small plastic-wrapped balls of narcotics removed from the terminal ileum by the author (D.C.E.) in a prisoner who was smuggling drugs by body packing. The patient developed an acute complete small bowel obstruction requiring emergent laparotomy. We performed a simple enterotomy in the ileum that was closed with interrupted silk sutures.

When it comes to IIFO-related gastrointestinal tract perforations, certain generalizations can be borrowed from the cumulative experience with non-intentional foreign object ingestions. In that setting, perforations

of the stomach, duodenum, and large intestine tend to present with slow onset of non-specific clinical signs while perforations of the ileum and jejunum typically are severe and acute[22]. This is likely due to foregut and hindgut perforations occurring in retroperitoneal spaces where perforations are often contained. In contrast, midgut perforations are more likely to result in free spillage of enteric contents into the abdomen.

PREVENTION

Recently published data reinforce the critical importance of prevention in the setting of IIFO, especially when repeated episodes of ingestion are present[2,5]. It has been difficult to prevent psychologically ill patients from ingesting foreign bodies and psychiatric medication has proven ineffective. Prisoners typically receive mental health care in their institution and do not require admission to the hospital for psychiatric care. Many of these patients are not suicidal and their psychiatric illness is not acute in nature, so psychiatric hospital admission is typically of little value[19]. Prevention strategies suggested include decreasing access to objects in the environment, increasing psychotherapy, changing diet for those with a history of food impaction, and dilating the esophagus for those with stricture[7].

The impetus for prevention primarily stems from the association between escalating psychiatric illness and repeated ingestion episodes. The fact that patients with recurrent ingestion episodes tend to have more severe psychiatric illness (as evident by the increasing number of formal psychiatric diagnoses) supports the contention that early and aggressive psychiatric intervention may help curtail the escalation of this self-damaging behavioral pattern. Gitlin *et al*[24] present a fascinating discussion of the psychiatric aspects of IIFO and found that most IIFO cases in the general population are associated with malingering, psychosis, pica, or personality disorders[24]. Treatment should be tailored to the patient's specific psychiatric diagnosis[25]. Prisons may employ closely monitored units in combination with psychiatric care in an attempt to reduce this type of behavior.

Another impetus for aggressive prevention is that finding that the financial burden of IIFO also tends to escalate as this repetitive self-destructive behavior continues to recur[5]. As the complexity of care and frequency of surgical intervention increases in patients with a history of prior ingestions, so does the cost of care.

CONCLUSION

IIFO is a rare but complex and expensive disease in prisoners. Observation and endoscopy are common appropriate management strategies and surgery should be avoided when possible. For those patients who present with their first episode of IIFO, an intensive monitoring and prevention plan should be developed to reduce the risk of recurrent episodes. While more data on the types of prevention interventions and their effectiveness is needed, the pattern of escalation among the IIFO population certainly warrants organized, proactive approaches.

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REFERENCES

1 **O'Sullivan ST**, Reardon CM, McGreal GT, Hehir DJ, Kirwan WO, Brady MP. Deliberate ingestion of foreign bodies by institutionalised psychiatric hospital patients and prison inmates. *Ir J Med Sci* 1996; **165**: 294-296 [PMID: 8990660 DOI: 10.1007/BF02943095]

2 **Dalal PP**, Otey AJ, McGonagle EA, Whitmill ML, Levine EJ, McKimmie RL, Thomas AC, Cook CH, Papadimos TJ, Reilley TE, Bergese SD, Steinberg SM, Stawicki SP, Evans DC. Intentional foreign object ingestions: need for endoscopy and surgery. *J Surg Res* 2013; **184**: 145-149 [PMID: 23726238 DOI: 10.1016/j.jss.2013.04.078]

3 **Weiland ST**, Schurr MJ. Conservative management of ingested foreign bodies. *J Gastrointest Surg* 2002; **6**: 496-500 [PMID: 12023005 DOI: 10.1016/S1091-255X(01)00027-0]

4 **Barros JL**, Caballero A, Rueda JC, Monturiol JM. Foreign body ingestion: management of 167 cases. *World J Surg* 1991; **15**: 783-788 [PMID: 1767546 DOI: 10.1007/BF01665320]

5 **Otey JA**, Houser JS, Jones C, Evans DC, Dalal PP, Whitmill ML, Levine EJ, McKimmie RL, Papadimos Steinberg SM, Bergese SD, Stawicki SP. Examination of financial charges associated with intentional foreign body ingestions by prisoners: A pattern of escalation. *OPUS 12 Scientist* 2014: **8**: 6-8. Available from: URL: http://journal.opus12.org/o12-ojs/ojs-2.1.1/index.php/o12sci/article/viewFile/286/123

6 The Pew Charitable Trusts Managing Prison Health Care Spending. May 15, 2014. Available from: URL: http://www.pewtrusts.org/en/research-and-analysis/reports/2014/05/15/managing-prison-health-care-spending

7 **Grimes IC**, Spier BJ, Swize LR, Lindstrom MJ, Pfau PR. Predictors of recurrent ingestion of gastrointestinal foreign bodies. *Can J Gastroenterol* 2013; **27**: e1-e4 [PMID: 23378983]

8 **Selivanov V**, Sheldon GF, Cello JP, Crass RA. Management of foreign body ingestion. *Ann Surg* 1984; **199**: 187-191 [PMID: 6696536 DOI: 10.1097/00000658-198402000-00010]

9 **Burton DM**, Stith JA. Extraluminal esophageal coin erosion in children. Case report and review. *Int J Pediatr Otorhinolaryngol* 1992; **23**: 187-194 [PMID: 1563936 DOI: 10.1016/0165-5876(92)90056-U]

10 **Bennett DR**, Baird CJ, Chan KM, Crookes PF, Bremner CG, Gottlieb MM, Naritoku WY. Zinc toxicity following massive coin ingestion. *Am J Forensic Med Pathol* 1997; **18**: 148-153 [PMID: 9185931 DOI: 10.1097/00000433-199706000-00008]

11 **Reilly J**, Thompson J, MacArthur C, Pransky S, Beste D, Smith M, Gray S, Manning S, Walter M, Derkay C, Muntz H, Friedman E, Myer CM, Seibert R, Riding K, Cuyler J, Todd W, Smith R. Pediatric aerodigestive foreign body injuries are complications related to timeliness of diagnosis. *Laryngoscope* 1997; **107**: 17-20 [PMID: 9001259 DOI: 10.1097/00005537-199701000-00006]

12 **Ohio Department of Rehabilitation and Correction DRC Annual Reports**. Accessed 8/6/2014 2006-2013. Available from: URL: http://www.drc.ohio.gov/web/reports/reports2.asp

13 **Blaho KE**, Merigian KS, Winbery SL, Park LJ, Cockrell M. Foreign body ingestions in the Emergency Department: case reports and review of treatment. *J Emerg Med* 1998; **16**: 21-26

[PMID: 9472755]
14 **Velitchkov NG**, Grigorov GI, Losanoff JE, Kjossev KT. Ingested foreign bodies of the gastrointestinal tract: retrospective analysis of 542 cases. *World J Surg* 1996; **20**: 1001-1005 [PMID: 8798356 DOI: 10.1007/s002689900152]
15 **Karp JG**, Whitman L, Convit A. Intentional ingestion of foreign objects by male prison inmates. *Hosp Community Psychiatry* 1991; **42**: 533-535 [PMID: 2060920]
16 **Karp JG**, Whitman L, Convit A. Ingestion of sharp foreign objects. *Am J Psychiatry* 1991; **148**: 271-272 [PMID: 1987829]
17 **Lee TH**, Kang YW, Kim HJ, Kim SM, Im EH, Huh KC, Choi YW, Kim TH, Lee OJ, Jung UT. Foreign objects in Korean prisoners. *Korean J Intern Med* 2007; **22**: 275-278 [PMID: 18309687 DOI: 10.3904/kjim.2007.22.4.275]
18 **Bisharat M**, O'Donnell ME, Gibson N, Mitchell M, Refsum SR, Carey PD, Spence RA, Lee J. Foreign body ingestion in prisoners - the Belfast experience. *Ulster Med J* 2008; **77**: 110-114 [PMID: 18711632]
19 **Huang BL**, Rich HG, Simundson SE, Dhingana MK, Harrington C, Moss SF. Intentional swallowing of foreign bodies is a recurrent and costly problem that rarely causes endoscopy complications. *Clin Gastroenterol Hepatol* 2010; **8**: 941-946 [PMID: 20692368 DOI: 10.1016/j.cgh.2010.07.013]
20 **Ribas Y**, Ruiz-Luna D, Garrido M, Bargalló J, Campillo F. Ingested foreign bodies: do we need a specific approach when treating inmates? *Am Surg* 2014; **80**: 131-137 [PMID: 24480212]
21 **Palese C**, Al-Kawas FH. Repeat intentional foreign body ingestion: the importance of a multidisciplinary approach. *Gastroenterol Hepatol (N Y)* 2012; **8**: 485-486 [PMID: 23293561]
22 **Goh BK**, Chow PK, Quah HM, Ong HS, Eu KW, Ooi LL, Wong WK. Perforation of the gastrointestinal tract secondary to ingestion of foreign bodies. *World J Surg* 2006; **30**: 372-377 [PMID: 16479337 DOI: 10.1007/s00268-005-0490-2]
23 **Webb WA**. Management of foreign bodies of the upper gastrointestinal tract: update. *Gastrointest Endosc* 1995; **41**: 39-51 [PMID: 7698623 DOI: 10.1016/S0016-5107(95)70274-1]
24 **Gitlin DF**, Caplan JP, Rogers MP, Avni-Barron O, Braun I, Barsky AJ. Foreign-body ingestion in patients with personality disorders. *Psychosomatics* 2007; **48**: 162-166 [PMID: 17329611 DOI: 10.1176/appi.psy.48.2.162]
25 **Klein CA**. Intentional ingestion and insertion of foreign objects: a forensic perspective. *J Am Acad Psychiatry Law* 2012; **40**: 119-126 [PMID: 22396349]

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REVIEW

Therapeutic upper gastrointestinal tract endoscopy in Paediatric Gastroenterology

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Abstract

Since the first report of use of endoscopy in children in the 1970s, there has seen an exponential growth in published experience and innovation in the field. In this review article we focus on modern age therapeutic endoscopy practice, explaining use of traditional as well as new and innovative techniques, for diagnosis and treatment of diseases in the paediatric upper gastrointestinal tract.

Key words: Child; Pediatrics; Endoscopy; Gastroscopy; Intestinal polyps; Hemorrhage; Caustics; Gastrostomy; Mitomycin; Gastroesophageal reflux

Core tip: This is a comprehensive review on use of therapeutic upper gastrointestinal endoscopy for emergency and elective procedures in paediatric gastroenterology.

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INTRODUCTION

Significant advances have occurred in diagnostic and therapeutic paediatric endoscopy since the first report of its use in children in the 1970s. The last two decades has seen an exponential growth in published experience and innovation in the field of paediatric therapeutic endoscopic intervention in the upper gastrointestinal (GI) tract and is the subject of this review.

HISTORY

The first attempt to observe the living human body

directly through a tube was in 1805 when Philip Bozzini created an instrument known as a Lichtleiter (light guiding instrument) to examine the urinary tract, rectum and pharynx[1,2]. In 1853, Antoine Jean Desormeaux of France developed an instrument specially designed to examine solely the urinary tract and the bladder; he named it the "endoscope", and it was the first time this term was used in history[3,4].

The first gastroscopy is accredited to Adolf Kussmaul in 1868, a German physician, who enlisted the help of a professional sword swallower to pass a 47 cm long metal tube with a 13 millimetre diameter into his stomach[5]. It was not until 1881, that Johann von Mikulicz and his colleagues created the first rigid gastroscope for practical applications; unfortunately these gastroscopes were not flexible at all. Finally in 1932, Dr. Rudolph Schindler invented the first flexible gastroscope that allowed examinations even while the tube was bent[4]. However, the significant breakthrough in endoscopy occurred in the 1950s with the advent of glass fiber, with Basil Hirschowitz being credited with development of the first flexible fiber-optic endoscope in 1957[6]. Following these adaptations, endoscopy of the GI tract became a routine diagnostic and therapeutic tool throughout gastroenterology units around the world.

With reduction in its size in the early 1970s, a few paediatricians began to adopt this new tool to examine the upper digestive tract[7]. During the late 1970s, the diagnostic value of endoscopy was slowly replacing the requirement of contrast radiology in the paediatric setting[8,9]. Subsequently, the first commercially available slim scope became available, the Olympus GIF-P, which was used in a few select paediatric centres around the world. However it was not till 1981 when the first European workshop on paediatric gastrointestinal was held, that a dedicated scope for paediatric use was developed, Olympus GIF-XP, which had an outer diameter of 7.8 mm. Consequently, other models by Fuji and Pentax were developed for the developing paediatric market.

PAEDIATRIC ENDOSCOPES

There are no published data to guide recommendations for endoscope choice, so decisions are made on standard practice and experience. The techniques in paediatric gastroscopy are principally the same as in the adult field specific consideration needs to be given to the slight anatomical variations. The oesophagus of the newborn is about 10 cm in length and about 0.5 cm in diameter and the trachea that sits in front of this is easily compressible during gastroscopy. The antrum and proximal duodenum are also more angulated requiring a greater degree of tip deflection before intubation into the empty duodenum which has a diameter of 1 cm[10].

Endoscopes for paediatric cases are chosen on the basis of age and weight of the patient. Table 1 illustrates this, reflecting practice in paediatric gastroenterology units in Southampton and Sheffield. Table 2 shows the current paediatric scopes available.

Table 1 A guide to use of paediatric scopes according to weight

Weight (kg)	OGD	ERCP
< 2.5	⩽ 6 mm gastroscope	7.5 mm duodenoscope
2.5-10	⩽ 6 mm gastroscope preferred. Standard gastroscopy may be considered particularly if endotherapy required	7.5 mm duodenoscope
10-35	Slim or Paediatric Gastroscope	*Via* slim or paediatric gastroscope
> 35	Standard	Most will tolerate standard therapeutic duodenoscope

INDICATIONS

Over the past few years, many organisations have attempted to identify selected criteria to create a list of indications for paediatric patients most likely to benefit from upper gastrointestinal tract endoscopy[11,12]. Because children undergo endoscopy less frequently than adults, the volume of evidence for its practice is limited compared to adults, nevertheless, there does remain a need for such guidelines. In essence, the decision to perform an endoscopy is based on whether it will alter diagnosis, treatment or prognosis. However, local expertise and availability of the test along with its cost can play an influential part in the decision making process. The most common indications for diagnostic and therapeutic endoscopy in the paediatric setting are listed in Table 3.

Recurrent abdominal pain or upper gastrointestinal bleeding account for the most common indications in the "Eastern" world[13-15] and abdominal pain and failure to thrive in the Western world[16-18].

INTERVENTIONAL ENDOSCOPY

The role of therapeutic intervention in the paediatric upper gastrointestinal tract can be divided broadly into (1) emergency and (2) elective procedures.

Emergency procedures

The two most common scenarios faced by the paediatric gastroenterologist is foreign body ingestion in the upper gastrointestinal tract (for example inanimate objects or food bolus and upper gastrointestinal tract bleeding. We discuss this further below.

Foreign body removal (Figures 1 and 2): As the child grows, explores and interacts with their local habitat they inevitably put foreign bodies into their mouths, ingesting a small proportion of them. Of over a 100000 cases of foreign body ingestion in the United

Table 2 Current paediatric endoscopes available

Manufacturer	Model	Insertion tube length/diameter (mm)	Definition/magnification/colour enhancement	Biopsy channel diameter (mm)
Olympus	GIF-N180	1100/4.9	Standard/none/NBI	2.0
	GIF-XP180N	1100/5.5	Standard/none/NBI	2.0
Fujinon	EG530N	1100/5.9	High-definition/zoom/none	2.0
	EG530NP	1100/4.9	High-definition/zoom/none	2.0
Pentax	EG1690K	1100/5.4	Standard/zoom/iSCAN	2.0
	EG1870K	1050/6.0	Standard/zoom/iSCAN	2.0

Adapted table from ASGE equipment for paediatric endoscopy status evaluation report.

Table 3 Indications for upper gastrointestinal endoscopy

Diagnostic
Recurrent abdominal pain (differentiation from FGIDs is important)
Weight loss/failure to thrive not just due to lack of nutrition
Dysphagia
Diarrhoea/malabsorption (differentiation from FGIDs is important)
Continued vomiting/haematemesis other than a simple
Mallory-Weiss tear
Investigation for iron deficiency anaemia
Suspected enteropathy-coeliac (new guidelines)/autoimmune
Part of investigations for inflammatory bowel disease
Therapeutic
Foreign body removal
Insertion of feeding tube
Dilation of strictures
Injection/banding varices
Treatment with Botox
Excision of polyps

States each year, more than 80% occur in children, mainly between the ages of 6 mo and 3 years[19-21]. Fortunately most foreign bodies that enter, pass through the gastrointestinal tract spontaneously, with only about 10%-20% requiring endoscopic removal and less than 1% require surgical removal[19,22]. Deaths are extremely rare but they have been reported[21,23]. The types of objects vary with geography but in the western world, coins are the most frequently encountered foreign body, while in the eastern world, fish bones account for a greater percentage[21,24]. Objects such as batteries or safety pins can add a degree of complexity and risk to foreign body retrieval.

After initial workup with a detailed history and biplane X-rays (antero-posterior and lateral), intervention depends on three factors; (1) the object ingested (2) location of the object and (3) the age of the patient. The location is often in areas of physiological narrowing; the upper oesophageal sphincter, the level of the aortic arch, lower oesophageal sphincter or the dependent part of the stomach, usually the gastric fundus[22,25]. It is important to note that the location of the pain or symptom does not always correlate with the associated site of impaction (visceral innervation)[26]. In the very young, due to the compressibility of the trachea, endoscopists need to be aware that even relatively small objects can potentially cause serious tracheal compression leading to respiratory compromise[10].

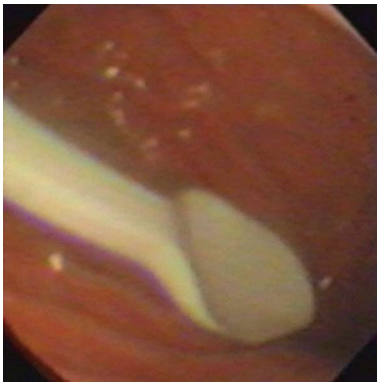

Figure 1 Foreign body (a plastic spoon) in the stomach of a child. Ingestion of coins and small lithium batteries tend to be much more common.

There are various methods to remove foreign bodies, with the flexible gastroscope being preferred as it allows direct visualisation, manipulation and observation of any potential injury to the adjacent mucosa[27,28]. The endoscopist should have an array of equipment readily available including polyp snares, alligator forceps, rat-tooth forceps, net baskets and overtubes.

Magill forceps, angled forceps commonly used in anaesthesia, are sometimes sufficient to remove a variety of objects in the oropharynx or upper oesophagus providing direct vision is possible. This may require the use of general anaesthesia and a laryngoscope to gently open up the oesophagus[29].

The use of a rubber or plastic dilator (Bougienage) may be used for foreign bodies impacted beyond the reach of forceps in the oesophagus to aid their passage into the stomach. However, careful consideration needs to be taken to assess that the object is judged able to pass along the oesophagus into the stomach without causing significant mucosal injury (*e.g.*, blunt and small objects such as coins) The use of this technique is thus limited and most endoscopists would only advocate this in experienced hands and only in patients where there has been witnessed ingestion within 24 h without existing oesophageal disease[30,31].

An alternative method is extracting the object impacted in the oesophagus with the use of a Foley catheter. This technique involves passing the Foley catheter past the foreign body and inflating the balloon with radio-opaque dye, then with fluoroscopic

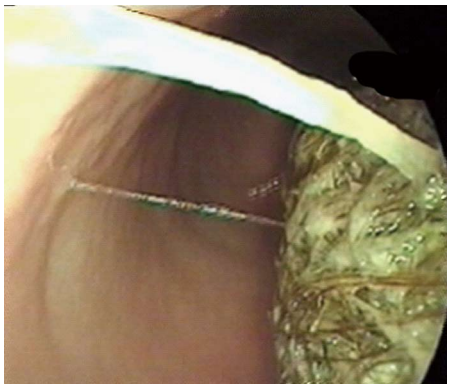

Figure 2 Bezoar seen at endoscopy. Endoscopic removal wasn't possible.

guidance, gently pulling on the catheter so the object is drawn back into the oral cavity and retrieved[32]. Many endoscopists do not advocate this technique in inexperienced hands as there is the risk of perforation or inadvertent placement of the foreign body into the trachea[33].

Pragmatically, foreign objects beyond the reach of forceps require intubation of the oesophagus with a flexible gastroscope. On entering the oesophagus, occasionally air insufflation or water flush alone may be sufficient to dislodge certain foreign objects to pass the lower oesophageal sphincter into the stomach. Smooth, round objects such as coins or flat batteries can often, more easily, be grasped with alligator jaw forceps. Rubber tipped or specialised alligator forceps are available for the paediatric 2 mm channel.

Special mention needs to be made regarding "button" batteries which are now ever more increasingly being swallowed[34]. Although standard batteries can cause problems due to their size and from the leakage of caustic material, button batteries have the added risk of conducting electricity (as both poles are in direct contact with the mucosa) which can cause significant necrosis and potential perforation[35]. Hence, even if these small batteries are not causing direct impaction, if found anywhere in the upper gastrointestinal tract, they should be removed. The preferable technique is to use a Roth Net® and retracting the basket as far back into the endoscope as possible and removing the endoscope and the foreign body together in one sweep.

Up to 30% of objects ingested are "sharp" such as needles and pins[21]. Unfortunately, the majority of sharp pointed objects are not radio-opaque. Hence, if there is a clinical suspicion of ingestion of these objects, it is of the authors' opinion that they should all proceed to having an endoscopic assessment and retrieval. Forceps and snares are often suitable as retrieval devices, minimising potential mucosal injury on retraction. This can be achieved by either retrieving the foreign body with the sharp end trailing, using an overtube or even novel devices such as protector hoods on the end of the endoscope[36].

Food bolus: This does not occur as frequently as it does in the adult population (the most common cause of oesophageal foreign body in this group)[37]. The likelihood of there being an underlying oesophageal pathology is higher such as eosinophilic oesophagitis, achalasia or strictures[38].

The indications for intervention is the same as that of other foreign bodies and inability to swallow saliva always requires emergency endoscopy, otherwise there is a risk of aspiration.

The use of medication, for example glucagon, buscopan and proteolytic enzymes, although still being used in current practice lack any evidence and the true likelihood is that the bolus would have passed naturally anyway. Therefore, authors, do not advocate their use considering the associated side effect profile[39]. An overtube may facilitate multiple passes of the endoscope that may be required, but caution with its use needs to be considered, as mentioned earlier.

Methods of removal can be broken into two actions of either "pushing" of the bolus into the stomach or "extraction" of the bolus into the oral cavity. With each method the food may be extracted preferably whole or "piecemeal". Both methods have been proven to be effective but the former "pushing" method is less preferable considering the unknown potential of pathology distal to the food bolus[40,41]. "Piecemeal" removal can be achieved using alligator forceps, rat-tooth forceps or tripod forceps down the accessory channel facilitating safer "pushing" of contents into the stomach.

Certain food boluses are not easily broken down into smaller pieces, in which case suction can be used with the aid of a cap on the end of an endoscope. If one is not readily available, the friction fit adaptor from an oesophageal band ligation kit can be used, allowing suction to stabilise the food bolus at the distal end more securely before pulling it into the oral cavity[42]. The authors have a preference of using a Roth Net®, with the catheter gently placed alongside the bolus with the net then opened in direct vision carefully in a "to and fro" manner to accommodate the food bolus before angling the net from one wall to the other to then allow the bolus to be caught in the net and retrieved.

Upper gastrointestinal tract bleeding: Life threatening gastrointestinal bleeding in paediatrics is rare but it is important for the endoscopist to recognise when it occurs and act promptly. As this is encountered infrequently in most endoscopy units, much of the evidence for the use of various haemostatic methods in children is inferred from the adult population. It is the common practice for the authors to collaborate with adult gastroenterologists and paediatric surgeons in the case of a serious gastrointestinal bleed.

Bleeding in the upper gastrointestinal tract can arise from peptic ulcers, varices, Mallory-Weiss tears,

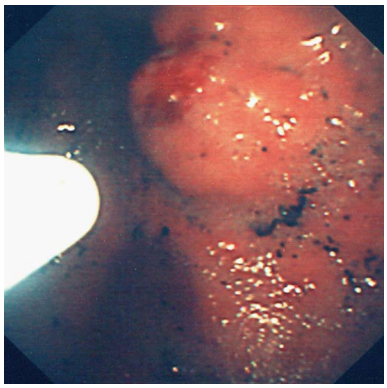

Figure 3 Injection of glue into a gastric varix.

dieulafoy lesions and angioectasia[43,44]. Unfortunately, there are no large series looking into gastrointestinal bleeding in children overall, with most large prospective studies assessing the incidence in the specialised paediatric intensive care setting[45]. Case series from Asia and developing countries show a higher incidence of variceal bleeding (mainly from extrahepatic portal hypertension) and those in developed countries having a higher incidence of erosive/peptic ulcer bleeding (mainly in the context of a a critically ill state)[45,46].

It is important for the endoscopist to be aware of the different modalities of endoscopic haemostasis available and it is just as important to know when these modalities would be required. Several scoring systems have been created in adults, although not validated in children, that can be used (after certain parameters are adjusted), to ascertain the need for endoscopic intervention. Blatchford and Rockall scores are used worldwide although there has been recent debate on their validity in the prediction of re-bleeding and 30 d mortality[47,48].

For peptic ulcers, the Forrest criteria was created for high-risk bleeding stigmata found during endoscopy. The presence of active bleeding, a non-bleeding visible vessel (re-bleeding rate of 40%-100%) or adherent clot (re-bleeding rate of approximately 25%) are indications for endoscopic treatment. While clean based ulcers do not require endoscopic therapy as the risk of re-bleeding is low (5%)[49,50]. Varices that are not actively bleeding can still be considered at high risk if there are signs of engorged protuberant vessels or a prominent red petechial mark on the vessel (cherry red spot) and therefore therapy should be considered.

The type of therapy used is dependent on the size of child, the type of lesion, the site of bleeding and the judgement and ability of the endoscopist. Three modalities are available to the endoscopist, which can be divided into 3 categories: injection, mechanical haemostasis or thermo-coagulation. Ideally, if the patient size permits, a two channel scope is preferable so that haemostasis can be achieved with concurrent use of flushing of the target area with saline for better visualisation.

(1) Injection therapy: Most injection needles have a small enough diameter to pass through a 2 mm channel in a paediatric gastroscope. Vasoactive agents, sclerosing agents and tissue adhesives can all be delivered by these needles.

Adrenaline is typically available in 1:10000 dilution and its action is *via* local vasoconstriction, platelet aggregation and mechanical tamponade[51]. In the case of an ulcer, it is important to wash the area, even if it is for a temporary view, in order to visualise the ulcer and identify a possible bleeding vessel. The scope is advanced near to the ulcer and the needle catheter fed through the channel. It is important to have the gastroscope close to the lesion or vessel as the extra length of catheter may predispose it to "kinking". Ideally, one should aim to inject 1-2 mls aliquots in 4 quadrants around the ulcer or near the vessel (so theoretically to exhibit its 3 effects circumferentially around the bleeding point). Unfortunately, no data exists for exact volumes in children as it does in adults where large volumes of 13-20 mls have been shown to be more efficacious[52].

Sclerosing agents such as sodium tetradecyl sulphate and ethanol act by inducing localised thrombosis over the bleeding vessel. In the past, sclerosing agents had been used for treatment of peptic ulcers and dieulafoy lesions[53]. In the last 2 decades, their role has been more confined to dealing with varices. Although band ligation is more efficacious in the adult population, the benefit of sclerosing agents in children is that they can be used in scenarios where band ligators are too large to pass through the oropharynx of a young child. The exact dose to use is not clear, but recent ASGE (American Society of Gastrointestinal Endoscopy) suggest the use of a quarter to half of what would be used in adults in children under the age of 12 years[54]. Injection can be delivered directly into the varix causing direct thrombosis or para-varix causing tamponade and submucosal fibrosis. Complications can occur including chest pain, mucosal ulceration and stricture formation. The largest case series to date was by Poddar *et al*[55] who demonstrated the use of alcohol injection in 257 children with varices and showed successful eradication in 95% of patients with a mean of 4.5 sessions (mean volume of 8 mls of absolute alcohol used). In this series 1.4% (n = 3) had perforation and 18% (n = 38) had stricture formation[55].

Tissue adhesives such as fibrin glue have emerged as being successful in adult treatment particularly for gastric varices (Figure 3)[56]. There is only one pilot study, to date, in the paediatric population by Rivet *et al*[57] where 8 infants were treated successfully for varices with fibrin glue. There are technical challenges with this agent, as there is a risk of the needle sticking to the varix or blocking the endoscope channel and causing serious damage. The authors' preference is to inject between 1-2 mls and flush thoroughly with

water and instead of bringing the injection needle back up the channel, to withdraw it together with the endoscope and cut the tip, hence preventing any adhesion to the scope.

(2) Mechanical therapy: Mechanical therapy in the form of clips is ever increasingly being utilised as it has the ability to effectively tamponade areas of bleeding. Its efficacy has been excellent in non variceal bleeding in adults, however published experience in the paediatric setting is lacking. Interestingly, a Japanese series has shown its benefit in prophylaxis. Eighty two children who underwent clipping of their varices, showed a prevention of variceal progression in 90%[58]. One of the limiting factors for its use is that all current brands on the market today need a channel size of 2.8 mm, therefore it is not compatible with paediatric gastroscopes. The jaw length of haemoclips range from 9-11 mm. Each brand has a slightly different clip deployment method, with the option of opening and closing the clips several times as well as clip rotation before deployment.

It is imperative that the endoscopist becomes familiar with the deployment technique. In the authors' experience, it is often the lack of communication between the endoscopist and assistant that leads to unsuccessful clip deployment. Indications for clip deployment are mainly for a bleeding vessel in an ulcer base, dieulafoy lesion or bleeding from Mallory-Weiss tears. It is the authors' preference to use a set of commands consisting of: (1) expose (exposing the clip from sheath); (2) open (opening jaws of clip); (3) close (closing of jaws); and (4) deploy (deploying the clip from the shaft). A useful pneumonic to remember is Extreme OCD (expose-open-close-deploy). In a case of severe bleeding that subsequently requires angiography, the radiologist finds the clip a useful aid to identify the site of the bleeding vessel before coil placement.

Band ligation has been the mainstay of treatment for oesophageal variceal haemorrhage for the last 3 decades. It can be utilised for primary haemostasis or for prophylactic measures. The device consists of a cylindrical friction fit adapter cap which has a number of elastic ligating bands fitted around it. The adaptor is placed on the end of an endoscope (minimum tip of 8.5 mm required) and a thread connected to these bands is fed through the channel of the endoscope to a deploying handle positioned on top of the biopsy channel. After the endoscope is placed in the desired location, suction is applied to draw the varix (or other lesion) into the adaptor. The bands are deployed by rotation of the handle, ideally suction should be held for a further 2-3 s to allow the band to fully reach its maximum tension capacity. For varices, this should ideally occur near the GOJ and proceed proximally to avoid obstruction of views by the bands or inadvertent displacement. In contrast to adult studies, randomised control studies are lacking and when they have been undertaken, the sample sizes have been small. As such, there is no consensus on the best modality, although reports suggest fewer complication rates with bands than with sclerotherapy[59].

(3) Thermo-coagulation: Thermo-coagulation devices deliver thermal energy causing coagulation and desiccation which can lead to haemostasis. There are 2 types available, monopolar and bipolar. With monopolar devices, *e.g.*, hot biopsy forceps, an electrical current is passed through the probe tip and conducted through the patient through a grounding pad and back to the diathermy unit. The probe can be applied directly to a vessel until bleeding stops. However, the authors do not use this routinely for haemostasis as the depth of burn is difficult to regulate and a deep thermal injury or perforation is possible[60].

A preferable method is bipolar coagulation. Here, the probe delivers thermal energy by creating an electrical circuit between 2 electrodes on the probe tip. Therefore, the electrical current passes through the affected tissue only, so tissue penetration is less deep. There are 5-French heater probes that can be used with paediatric gastroscopes. Bipolar probes have 6 points through which current can be passed and hence good tissue contact can be made, whether it is used en face or tangentially. As it has less tissue penetration, more pressure is required for deeper penetration and application time is longer. From the authors' experience when haemostasis is not achieved, it is often when the endoscopist has not taken enough time to place the tip on the bleeding point, which should be a minimum of about 10 s for a bleeding vessel or 3-4 s for angioectasia.

Heater probes have an electrical heated coil inside a Teflon-covered insulated cylinder. Coagulation is performed by directly applying heat through the probe over the bleeding vessel with pressure. There is very little experience of this in paediatrics and currently no probe available for paediatric scopes.

Argon plasma coagulation (APC) is a non-contact form of coagulation in which current is transmitted in an arc of electricity through an ionised gas (argon). It has been shown to be useful in adults for non-variceal bleeding and is commonly used in the treatment of radiation-induced proctitis[61]. The degree of coagulation is dependent on several factors: the power settings, duration of application, distance between tip and tissue and flow rate of the argon gas. Its advantages are that as the tissue coagulates, the conductivity decreases which hence limits the depth of injury and it is available in a 1.5 mm diameter probe for the paediatric gastroscope. There is only one case series of its use in children by Khan *et al*[62] where 13 children with upper GI lesions (ulcers, haemangiomas and erosions) were successfully treated with APC (flow rate of 0.9 L/min and power at 55 w). Care should be taken to aspirate the argon gas frequently which is potentially combustible in large volumes.

Elective procedures

As experience grows in this evolving field, the range of indications for "chronic" conditions suitable for therapeutic intervention increases. We list a few of these used in common practice as well as some novel therapies.

Percutaneous endoscopic gastrostomy

This is now very commonly used since it was first performed by Gauderer *et al*[63] in 1979. To this day, it is still an effective method of feeding *via* the stomach where the oral route may not be possible, providing hydration and nutrition[64]. Endoscopic gastrostomy placement compared to surgical placement was developed to avoid surgical intervention. The most common indications for its use in the paediatric setting are neurological impairment or failure to thrive[65,66]. Percutaneous endoscopic gastrostomy (PEG) use is based around the fact that the continuous, suture-less approximation of the stomach to the peritoneum and anterior abdominal wall by a feeding tube leads to the formation of adhesional attachments which subsequently leads to the formation of a tract around the tube[66].

Several modifications of the technique have been introduced since it was first described. The "pull" technique is the most commonly used. This involves performing a gastroscopy to identify the anterior stomach and using sufficient air insufflation to oppose the anterior stomach with the anterior abdominal wall, pushing aside any possible visceral organs that may be inadvertently punctured. The area for insertion of the tube is ascertained by visualisation of trans-illumination of the gastroscope through the abdominal wall and visualisation of a clear finger indentation within the stomach lumen. This area is marked and sterilised before infiltration of local anaesthesia. A skin incision of approximately 0.5 cm is made (only few mm depth required) which can be made horizontally so the scar can be hidden within skin creases for aesthetic purposes. A trocar/angiocath is pushed through this point into the stomach under endoscopic vision. A soft guide wire is then inserted through this so that it just appears within the gastric lumen. This threading wire is then snared through the endoscope and the whole apparatus, scope, snare and thread are withdrawn together. After the guide wire is out, a suitable feeding tube is attached to it and pulled through the mouth and out of the incision. An external bolster/stopper is then placed on the skin to hold this in place. It is at discretion of the endoscopist whether it is necessary to re-intubate the scope to confirm placement of the tube.

The authors would advocate that the distance on the PEG tube is documented, *i.e.,* the distance from the "button/stopper" in the gastric end to that on the skin surface, markings which are available on all feeding tubes. This distance varies according to the size of the child, however, it may be a guide in cases where a larger than expected distance is noted to suggest a possible additional inadvertent visceral attachment. Antibiotics should always be given although the optimal timing, whether pre, post or peri can be left to local microbiology policies.

Oesophageal dilatation: Unlike in adults, where malignancy is the major cause of upper gastrointestinal structuring, in children it is almost always caused by benign disorders. Techniques and equipment used in adult patients can be applied to children, *i.e.*, bougienage, balloon dilatation and self-expanding stents (seldom used). The approach will be determined as with many cases where adult skills are transferred to the paediatric setting by characteristics of the stricture, position, size (both radial and longitudinal), availability of equipment, expertise of the endoscopist and patient size.

The most common cause of oesophageal stricturing worldwide is the ingestion of caustic liquids from around the house, with the other major causes falling into peptic or post-surgical strictures (mainly corrective surgery for oesophageal atresia)[67]. Rarer conditions involve the consequences of prolonged ingestion of certain foreign bodies, strictures associated with eosinophilic oesophagitis, post variceal sclerotherapy and congenital abnormalities.

Dilatation is indicated in patients with symptomatic obstruction. Anastomotic strictures post oesophageal atresia are common, with an incidence of up to 44% in some series[68,69]. Koivusalo *et al*[70] demonstrated that a watch and wait policy based on symptomatology was superior to routine dilatations as greater than half did not require any subsequent dilatations[70].

The purpose of oesophageal dilatation is to alleviate symptoms, permit free intake of enteral nutrition and reduce complications such as pulmonary aspiration. This must be weighed up against the risk of perforation. This has been reported as 0%-5% after balloon dilatation and 8%-9% after bougienage[71,72].

Bougie dilators come in a range of makes and diameters. However, in the paediatric setting experience is mainly with Savary-Gillard type systems, *i.e.,* a long tapered, radio-opaque, wire-guided and poly-vinyl hollow tubes designed for use in the oesophagus. The bougie system is naturally limited to the oesophagus in the upper GI tract as transmission of the force more distally would be more difficult. Bougie dilators apply axial as well as radial forces[73]. They come in sizes of 5-20 mm diameter and 70-100 cm in length. The technique involves feeding a guide wire through the lumen of the stricture either endoscopically, fluoroscopically or both. When done solely endoscopically, it is worthwhile to note the distance of the stricture from the incisors. After the endoscope is retracted, it is imperative, particularly if fluoroscopy is not used, to maintain the guide wire in a fixed position by an assistant so it does not inadvertently move out of position. The bougie is lubricated well and passed over the guide wire until the maximal diameter has passed

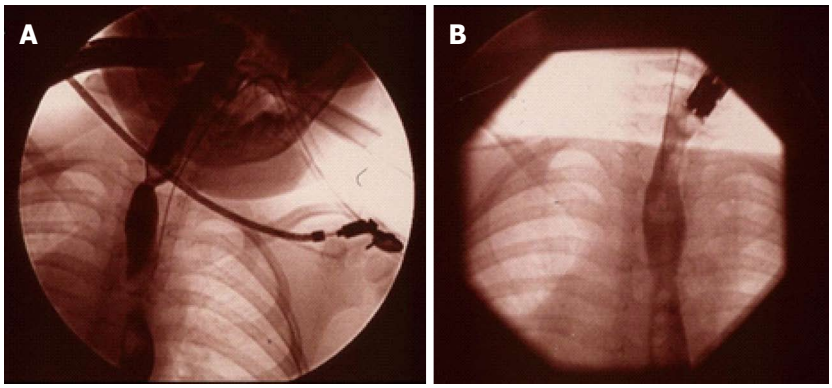

Figure 4 (A) Videofluoroscopy image of a proximal and a distal stricture in the oesophagus and (B) resolution of the strictures in the same child 3 mo after treatment with Mitomycin C.

over the area of the stricture (as estimated from the previous incisor distance). In adults, it is advocated that only 3 dilators or a maximum increment of 3 mm from initial dilatation occurs in a single session to minimise risk of oesophageal perforation[74]. This data is lacking in children and hence an estimate of the diameter of the adjacent normal calibre oesophagus should be used.

Balloon dilators have the benefit of potentially being used under direct vision and delivering direct radial force across the entire stricture, while controlled manometrically by a hand held device by an assistant. It cannot be passed down the standard 2.0 mm channel of a paediatric scope but in these scenarios, guide wires can be placed *via* fluoroscopy to enable the balloon catheter to pass over this[75,76]. Balloons are available in 4-40 mm diameter and length varying depending on location used. With this range is mind, in infants, larger length balloons may traverse unnecessarily the entire length of the oesophagus so shorter lengths, pyloric or colonic, should be used in this group. The ideal length of time the balloon is inflated is not known but it is the authors' experience to leave it inflated for at least 1 min.

One of the issues with caustic strictures is the frequency of stricture recurrence after dilatation. The authors reported the first use of Mitomycin-C, an antifibrotic agent, for treatment of caustic strictures (Figure 4)[77]. Following the initial report, a case series was reported from 8 paediatric gastroenterology centres around the world about its successful use[78] and it has now been adopted as standard practice in many units[78,79].

Choice of methods for dilatation is largely down to the experience of the endoscopist and it is not known if one method is better over another for any particular indication. In retrospective data of oesophageal atresia patients, balloons were found to be more effective than bougienage and required fewer dilatations[79]. However, another report showed those with peptic and caustic strictures did better with bougienage[80]. Balloon dilatation does seem to offer a better safety profile and better efficacy[79]. Perforations are a risk although this can be minimised by cautious and gentle dilatation, and avoidance of excessive manipulation that may cause potentially damaging shearing axial forces.

Gastroesophageal reflux disease-novel therapies: The burden of gastro-oesophageal reflux (GORD) is well established in adults with all its associated symptoms including chest discomfort, recurrent cough, chronic respiratory disorders and regurgitation. In the paediatric setting, the additional sequelae of failing to thrive are seen which reduces the threshold for intervention. Those children with frequent symptoms under the age of 2 are more likely to have symptoms later in their childhood[81].

The predominant mechanism causing GORD, as in the adult population, is transient lower oesophageal sphincter (LES) relaxation. This is defined as an abrupt and transient decrease in LES pressure to the level of intra-gastric pressure, unrelated to swallowing and of relatively longer duration than the relaxation triggered by a swallow[82].

The aim of treatment for GORD is to achieve symptom relief whilst preventing complications. Those patients who fail to achieve control with medical therapy or not wishing to be dependent on long term anti-reflux medications may warrant an anti-reflux surgical procedure[83,84].

A variety of endoscopic techniques have been developed for treatment of GORD. These methods can be divided in three broad categories: (1) methods that attempt to create a fundoplication/gastroplication (plicating techniques); (2) methods that create a controlled stricture (radio frequency); and (3) methods that bulk the gastro-oesophageal junction (injecting bulking agents)[85]. There is only experience in the paediatric setting with the first two methods. The ideal procedure should be safe, effective over a long term and should not compromise future surgical options.

Endoluminal gastroplication (Figures 5-7): Endoluminal plication uses mechanical techniques to decrease reflux by approximation of tissue at

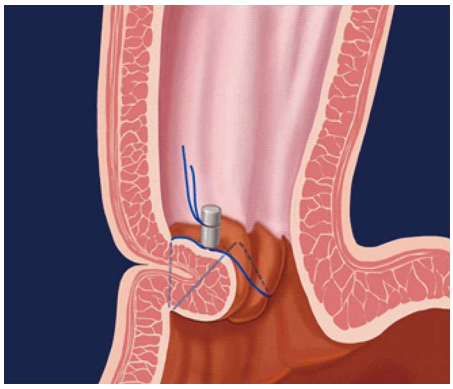

Figure 5 Endoscopic gastroplication. This figure the pattern of a zig-zag stich when applied with an Endocinch® sewing maching.

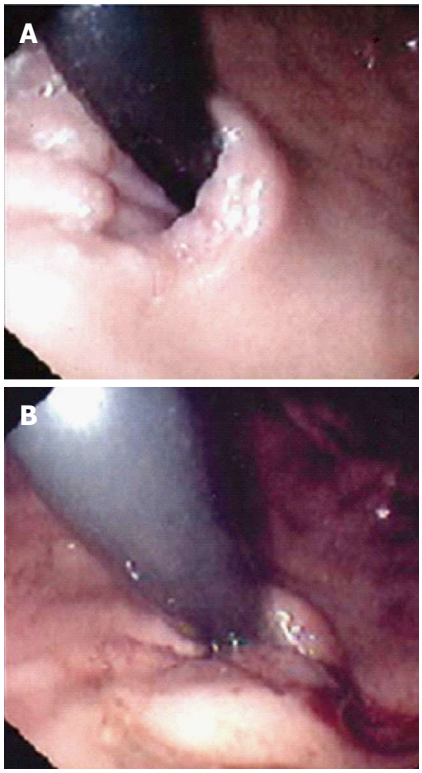

Figure 6 Endoscopic view (J manoeuvre) of a lax Gastro-Oesophageal junction in a child with major reflux before (A) and after (B) application of stitch with the EndoCinch®.

or below the Gastro-Oesophageal junction (GOJ). The main plication device be used with the authors' experience is the EndoCinch® (CR BARD Endoscopic technologies, Massachusetts, United States). This was initially developed by Swain *et al*[86] in London United Kingdom, in the mid-1980s, and was the first Federal Drug Agency (FDA) approved endoscopic sewing machine method for treating GORD[86].

The method involves placement of an overtube to facilitate repeat intubations that are required for the procedure. An endoscope with a capsule-shaped plication device (with a side hole) mounted at the tip is inserted to the level of the squamo-columnar junction

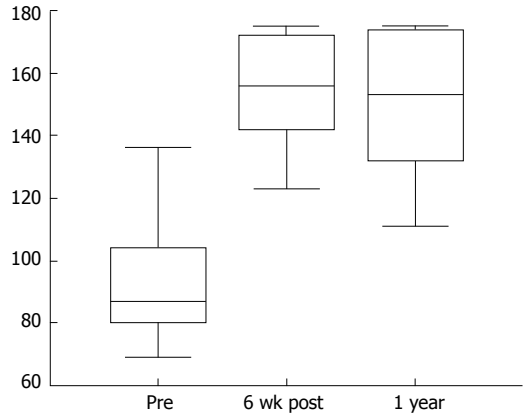

Figure 7 Significant improvement in the total QOLRAD scores (Quality of life in reflux and dyspepsia), 6 wk and 1 year after gastroplication with the Endocinch®.

through the overtube, where the side hole is brought into close contact with the wall to draw the mucosa into the capsule with the aid of air suction. A puncture needle with a non-absorbable suture attached (suture tag), is inserted into the biopsy channel and is then passed through. The suction pressure is released and the capsule is carefully rotated away from the stitch side. A suture tag is then set up in the endoscope again and a second set of sutures is placed following the same procedure at a position rotated between 30 and 60 degrees away from the first set. The two sutures form a plication using a knotting device that is inserted into the biopsy channel of a separate endoscope and the process is completed by plicating the tissue in the form of a pouch. The second and third plications are performed in either a linear or circumferential manner, or a combination of the two, depending on the available area within the GOJ and position preference[87].

The procedure can be carried out as a day case, with studies showing it to be relatively quick, non-invasive, effective and safe. Results have been shown it to be comparable to laparoscopic fundoplication in adults[88-90].

The authors have a preference of placing two plication suture lines circumferentially, 1.5 cm below the GOJ and one 0.5 cm below the GOJ, which we believe to be superior to other methods used in adults[88,91]. In a series of 17 children with a median age 13 years, with GORD refractory or dependent on proton pump inhibitors, all patients showed an improvement in symptom severity, frequency and reflux related quality of life scores[92]. Fourteen patients (88%) at 1 year and 9 patients (56%) at 3 years remained without a need for any anti-reflux medication. A sustained improvement in heartburn, regurgitation and vomiting was seen at 3 years. Only one complication of gastric bleeding was observed which resolved spontaneously[93]. The duration of action is conflicting in adults and is under on-going

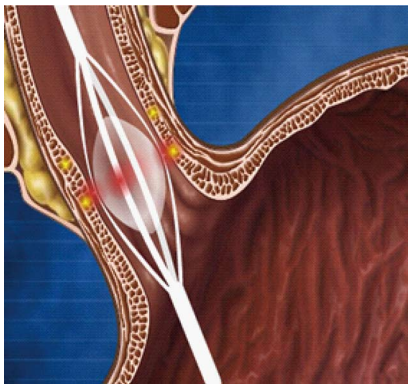

Figure 8 Use of a balloon to deliver radiofrequency energy *via* needle electrodes to the mucosa.

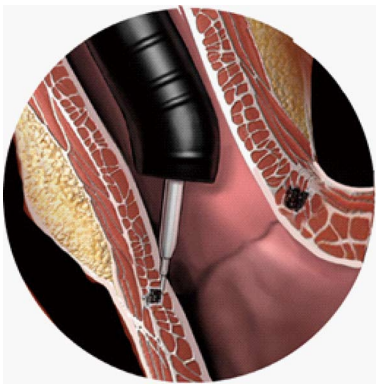

Figure 9 Injection of liquid polymer into the oesophageal mucosa. The Enteryx® procedure.

review[94-96]. However, there does appear to be superior efficacy in children and the reasons for this may be due to a relatively deeper suture depth in the thinner paediatric oesophagus[93].

Stricture formation through delivery of radio-frequency energy: Curon Medical designed the STRETTA® system (Figure 8) which gained FDA approval in 2000. The device employs a special balloon on a catheter with four needle electrodes. An upper GI endoscopy is undertaken first to identify the GOJ. A guide wire is then placed into the stomach, the endoscope is then removed and the STRETTA® catheter is then passed over, advancing the balloon to a position at the GOJ. The balloon is inflated and the electrodes are deployed to penetrate into the muscle layer. Radiofrequency energy is delivered through the electrodes to create thermal lesions radially at several levels in the lower oesophageal sphincter and gastric cardia[97]. As the lesions heal, it induces collagen tissue contraction, remodelling and modulation of the triggering threshold for transient LES relaxations[98].

Evidence for its benefit is promising, as shown in a recent meta-analysis including 1441 patients, although these results need to be interpreted with caution as there was significant heterogeneity between trials[99]. The largest randomised sham-control trial, to date, investigating 64 patients, revealed the radiofrequency group having significant improvement in heartburn symptoms (61% *vs* 33%) and GORD quality of life score (61% *vs* 30%) at 6 mo[100]. It is seldom associated with serious complications but there have been reports of delayed gastric emptying in a few[101].

There are only 2 reported case series in the paediatric setting. Islam *et al*[102] reported its first use in 6 teenagers (mean age 18, range 14-21) in those who had previous surgical reflux surgery. All had an improvement in their GORD symptom score with 5 out of 6 completely asymptomatic at 3 mo[102]. Liu *et al*[103] reported on 8 children aged 11-16, including 3 children with neurological impairment requiring a concomitant percutaneous gastrostomy feeding tube[103]. The follow-up period was up to 15 mo and 6 of the patients were considered to have a successful outcome, based on improvement of GORD symptoms and tolerability of feeding. Of the two failures, one required continued PPI use and the other a Nissen fundoplication.

Without larger published series in children to date, paediatric gastroenterologists are likely to be reserved in its use, particularly considering that it is unknown what the long-term effects of thermal injury to the GOJ in a child is likely to be.

Another novel endoscopic treatment, the ENTERYX procedure involves injecting a gastro-esophageal biopolymer into the lower oesophageal sphincter (Figure 9). The authors do not recommended its use in paediatric practice though. Besides concerns regarding long-term outcome of the ENTERYX injection, perforation of the oesophagus is a risk during administration of this treatment.

Assessment and excision of upper GI polyps: Over the last few years, investigation of number of polyposis syndromes has revealed the presence of upper GI polyps in addition to the more widely documented colorectal polyps. The most common polyposis syndrome, familial adenomatous polyposis (FAP) is an inherited autosomal dominant condition which results from mutations within the gene locus on chromosome 5[104]. In addition to causing the development of numerous colorectal polyps in FAP patients, it has also been found that multiple polyps may occur in the gastric antrum and duodenum[105-108]. Domizio *et al*[109], investigating a series of patients from St Mark's Hospital, demonstrated microscopic gastroduodenal pathology in 100/102 asymptomatic FAP patients. This included the presence of duodenal adenomas in 94 patients and gastric fundic gland polyps in 44 patients. Although the significance and natural history of gastric polyps in patients with polyposis syndromes has not been clearly described, it has been shown that patients with FAP have a higher risk of duodenal cancer and various methods of upper GI endoscopic assessment tools have been used

including standard endoscopy, endoscopy with a side-viewing scope and double-balloon enteroscopy[110,111].

In addition to FAP, other syndromes are known to predispose to upper GI polyps which can pose management challenges. It is known that children with Peutz-Jeghers (PJ) syndrome have a risk of polyps which can lead to harmful consequences like bleeding and obstruction. Children with PJ may often have to undergo laparotomies to manage these problems but increasingly less invasive, endoscopic management options are being used like balloon enteroscopy which can even be used to remove polyps in the proximal jejunum[112].

CONCLUSION

As experience grows in therapeutic interventions in the upper GI tract, treatment that was once considered pioneering is becoming relatively routine. Systems are now in place to develop training in this continually evolving speciality to allow expertise to develop. The current disparity between paediatric and adult endoscopy is likely to become narrower in the near future.

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REFERENCES

1 **Rathert P**, Lutzeyer W, Goddwin WE. Philipp Bozzini (1773-1809) and the Lichtleiter. *Urology* 1974; **3**: 113-118 [PMID: 4591408]
2 **Bozzinin P**. Lichtleiter eine Enfindung zur Auschschauung innere Theieler und Krankheiten. *Journal der Practischen Arzneykunde und Wunderartzney kunst* 1806; **24**: 107-124
3 **Desormeaux AJ**. De l'Endoscopie, instrument propre a'eclairer certaines cavities interieures de l'economie. *Compterendus de L' Academie des Sciences* 1855; 692-693 Abstract
4 **Spaner SJ**, Warnock GL. A brief history of endoscopy, laparoscopy, and laparoscopic surgery. *J Laparoendosc Adv Surg Tech A* 1997; **7**: 369-373 [PMID: 9449087]
5 **Pellicano R**, Bocus P, De Angelis C. Adolf Küssmaul, the sword eater and modern challenges of digestive endoscopy. *Minerva Gastroenterol Dietol* 2011; **57**: 109-110 [PMID: 21587141]
6 **Hirschowitz BI**. Endoscopic examination of the stomach and duodenal cap with the fiberscope. *Lancet* 1961; **1**: 1074-1078 [PMID: 13714621]
7 **Cadranel S**, Rodesch P, Peeters JP, Cremer M. Fiberendoscopy of the gastrointestinal tract in children. A series of 100 examinations. *Am J Dis Child* 1977; **131**: 41-45 [PMID: 299976]
8 **Lux G**, Rösch W, Phillip J, Frühmorgen P. Gastrointestinal fiberoptic endoscopy in pediatric patients and juveniles. *Endoscopy* 1978; **10**: 158-163 [PMID: 699880 DOI: 10.1055/s-0028-1098284]
9 **Kessler E**, Chappell JS. Upper gastro-intestinal endoscopy in chidren. *S Afr Med J* 1979; **56**: 591-593 [PMID: 550408]
10 **Barth BA**, Banerjee S, Bhat YM, Desilets DJ, Gottlieb KT, Maple JT, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Song LM, Rodriguez SA. Equipment for pediatric endoscopy. *Gastrointest Endosc* 2012; **76**: 8-17 [PMID: 22579260 DOI: 10.1016/j.gie.2012.02.023]
11 **Squires RH**, Colletti RB. Indications for pediatric gastrointestinal endoscopy: a medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1996; **23**: 107-110 [PMID: 8856574]
12 **Lee KK**, Anderson MA, Baron TH, Banerjee S, Cash BD, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO, Jagannath SB, Lichtenstein D, Shen B, Fanelli RD, Van Guilder T. Modifications in endoscopic practice for pediatric patients. *Gastrointest Endosc* 2008; **67**: 1-9 [PMID: 18155419 DOI: 10.1016/j.gie.2007.07.008]
13 **Joshi MR**, Sharma SK, Baral MR. Upper GI endoscopy in children- in an adult suite. *Kathmandu Univ Med J (KUMJ)* 2005; **3**: 111-114 [PMID: 16415605]
14 **Karim B**. Upper gastrointestinal endoscopy in children - an experience at a paediatric gastroenterology unit. *Mymensingh Med J* 2003; **12**: 124-127 [PMID: 12894047]
15 **Ng DK**, Liu JH, Ho JC. Paediatric upper gastrointestinal endoscopy: a 2-year review. *Chin Med J (Engl)* 1997; **110**: 587-589 [PMID: 9594258]
16 **Sheiko MA**, Feinstein JA, Capocelli KE, Kramer RE. Diagnostic yield of EGD in children: a retrospective single-center study of 1000 cases. *Gastrointest Endosc* 2013; **78**: 47-54.e1 [PMID: 23669024 DOI: 10.1016/j.gie.2013.03.168]
17 **Zahavi I**, Arnon R, Ovadia B, Rosenbach Y, Hirsch A, Dinari G. Upper gastrointestinal endoscopy in the pediatric patient. *Isr J Med Sci* 1994; **30**: 664-667 [PMID: 8045755]
18 **Thakkar K**, El-Serag HB, Mattek N, Gilger MA. Complications of pediatric EGD: a 4-year experience in PEDS-CORI. *Gastrointest Endosc* 2007; **65**: 213-221 [PMID: 17258979 DOI: 10.1016/j.gie.2006.03.015]
19 **Wyllie R**. Foreign bodies in the gastrointestinal tract. *Curr Opin Pediatr* 2006; **18**: 563-564 [PMID: 16969173 DOI: 10.1097/01.mop.0000245359.13949.1c]
20 **Little DC**, Shah SR, St Peter SD, Calkins CM, Morrow SE, Murphy JP, Sharp RJ, Andrews WS, Holcomb GW, Ostlie DJ, Snyder CL. Esophageal foreign bodies in the pediatric population: our first 500 cases. *J Pediatr Surg* 2006; **41**: 914-918 [PMID: 16677882 DOI: 10.1016/j.jpedsurg.2006.01.022]
21 **Cheng W**, Tam PK. Foreign-body ingestion in children: experience with 1,265 cases. *J Pediatr Surg* 1999; **34**: 1472-1476 [PMID: 10549750]
22 **Uyemura MC**. Foreign body ingestion in children. *Am Fam Physician* 2005; **72**: 287-291 [PMID: 16050452]
23 **Simic MA**, Budakov BM. Fatal upper esophageal hemorrhage caused by a previously ingested chicken bone: case report. *Am J Forensic Med Pathol* 1998; **19**: 166-168 [PMID: 9662114]
24 **Kay M**, Wyllie R. Pediatric foreign bodies and their management. *Curr Gastroenterol Rep* 2005; **7**: 212-218 [PMID: 15913481]
25 **Nandi P**, Ong GB. Foreign body in the oesophagus: review of 2394 cases. *Br J Surg* 1978; **65**: 5-9 [PMID: 623968]
26 **Louie JP**, Alpern ER, Windreich RM. Witnessed and unwitnessed esophageal foreign bodies in children. *Pediatr Emerg Care* 2005; **21**: 582-585 [PMID: 16160661]
27 **Gmeiner D**, von Rahden BH, Meco C, Hutter J, Oberascher G, Stein HJ. Flexible versus rigid endoscopy for treatment of foreign body impaction in the esophagus. *Surg Endosc* 2007; **21**: 2026-2029 [PMID: 17393244 DOI: 10.1007/s00464-007-9252-6]
28 **Katsinelos P**, Kountouras J, Paroutoglou G, Zavos C, Mimidis K, Chatzimavroudis G. Endoscopic techniques and management of foreign body ingestion and food bolus impaction in the upper gastrointestinal tract: a retrospective analysis of 139 cases. *J Clin Gastroenterol* 2006; **40**: 784-789 [PMID: 17016132 DOI: 10.1097/01.mcg.0000225602.25858.2c]
29 **Janik JE**, Janik JS. Magill forceps extraction of upper esophageal

coins. *J Pediatr Surg* 2003; **38**: 227-229 [PMID: 12596109 DOI: 10.1053/jpsu.2003.50049]
30 **Arms JL**, Mackenberg-Mohn MD, Bowen MV, Chamberlain MC, Skrypek TM, Madhok M, Jimenez-Vega JM, Bonadio WA. Safety and efficacy of a protocol using bougienage or endoscopy for the management of coins acutely lodged in the esophagus: a large case series. *Ann Emerg Med* 2008; **51**: 367-372 [PMID: 17933426 DOI: 10.1016/j.annemergmed.2007.09.001]
31 **Dahshan AH**, Kevin Donovan G. Bougienage versus endoscopy for esophageal coin removal in children. *J Clin Gastroenterol* 2007; **41**: 454-456 [PMID: 17450025 DOI: 10.1097/01.mcg.0000225-622.09718.5f]
32 **Schunk JE**, Harrison AM, Corneli HM, Nixon GW. Fluoroscopic foley catheter removal of esophageal foreign bodies in children: experience with 415 episodes. *Pediatrics* 1994; **94**: 709-714 [PMID: 7936900]
33 **Berggreen PJ**, Harrison E, Sanowski RA, Ingebo K, Noland B, Zierer S. Techniques and complications of esophageal foreign body extraction in children and adults. *Gastrointest Endosc* 1993; **39**: 626-630 [PMID: 8224682]
34 **Litovitz T**, Whitaker N, Clark L. Preventing battery ingestions: an analysis of 8648 cases. *Pediatrics* 2010; **125**: 1178-1183 [PMID: 20498172 DOI: 10.1542/peds.2009-3038]
35 **Maves MD**, Carithers JS, Birck HG. Esophageal burns secondary to disc battery ingestion. *Ann Otol Rhinol Laryngol* 1984; **93**: 364-369 [PMID: 6465778]
36 **Bertoni G**, Sassatelli R, Conigliaro R, Bedogni G. A simple latex protector hood for safe endoscopic removal of sharp-pointed gastroesophageal foreign bodies. *Gastrointest Endosc* 1996; **44**: 458-461 [PMID: 8905368]
37 **Mahesh VN**, Holloway RH, Nguyen NQ. Changing epidemiology of food bolus impaction: is eosinophili :c esophagitis to blame? *J Gastroenterol Hepatol* 2013; **28**: 963-966 [PMID: 23425056 DOI: 10.1111/jgh.12135]
38 **Hurtado CW**, Furuta GT, Kramer RE. Etiology of esophageal food impactions in children. *J Pediatr Gastroenterol Nutr* 2011; **52**: 43-46 [PMID: 20975581 DOI: 10.1097/MPG.0b013e3181e67072]
39 **Khayyat YM**. Pharmacological management of esophageal food bolus impaction. *Emerg Med Int* 2013; **2013**: 924015 [PMID: 23738071 DOI: 10.1155/2013/924015]
40 **Vicari JJ**, Johanson JF, Frakes JT. Outcomes of acute esophageal food impaction: success of the push technique. *Gastrointest Endosc* 2001; **53**: 178-181 [PMID: 11174288]
41 **Longstreth GF**, Longstreth KJ, Yao JF. Esophageal food impaction: epidemiology and therapy. A retrospective, observational study. *Gastrointest Endosc* 2001; **53**: 193-198 [PMID: 11174291]
42 **Mamel JJ**, Weiss D, Pouagare M, Nord HJ. Endoscopic suction removal of food boluses from the upper gastrointestinal tract using Stiegmann-Goff friction-fit adaptor: an improved method for removal of food impactions. *Gastrointest Endosc* 1995; **41**: 593-596 [PMID: 7672555]
43 **Dehghani SM**, Haghighat M, Imanieh MH, Tabebordbar MR. Upper gastrointestinal bleeding in children in Southern Iran. *Indian J Pediatr* 2009; **76**: 635-638 [PMID: 19390793 DOI: 10.1007/s12098-009-0092-3]
44 **Huang IF**, Wu TC, Wang KS, Hwang B, Hsieh KS. Upper gastrointestinal endoscopy in children with upper gastrointestinal bleeding. *J Chin Med Assoc* 2003; **66**: 271-275 [PMID: 12908568]
45 **Cochran EB**, Phelps SJ, Tolley EA, Stidham GL. Prevalence of, and risk factors for, upper gastrointestinal tract bleeding in critically ill pediatric patients. *Crit Care Med* 1992; **20**: 1519-1523 [PMID: 1424693]
46 **Yachha SK**, Khanduri A, Sharma BC, Kumar M. Gastrointestinal bleeding in children. *J Gastroenterol Hepatol* 1996; **11**: 903-907 [PMID: 8912124]
47 **Wang CH**, Chen YW, Young YR, Yang CJ, Chen IC. A prospective comparison of 3 scoring systems in upper gastrointestinal bleeding. *Am J Emerg Med* 2013; **31**: 775-778 [PMID: 23465874 DOI: 10.1016/j.ajem.2013.01.007]
48 **Dicu D**, Pop F, Ionescu D, Dicu T. Comparison of risk scoring systems in predicting clinical outcome at upper gastrointestinal bleeding patients in an emergency unit. *Am J Emerg Med* 2013; **31**: 94-99 [PMID: 23000328 DOI: 10.1016/j.ajem.2012.06.009]
49 **Forrest JA**, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974; **2**: 394-397 [PMID: 4136718]
50 **Heldwein W**, Schreiner J, Pedrazzoli J, Lehnert P. Is the Forrest classification a useful tool for planning endoscopic therapy of bleeding peptic ulcers? *Endoscopy* 1989; **21**: 258-262 [PMID: 2693077 DOI: 10.1055/s-2007-1010729]
51 **Park WG**, Yeh RW, Triadafilopoulos G. Injection therapies for nonvariceal bleeding disorders of the GI tract. *Gastrointest Endosc* 2007; **66**: 343-354 [PMID: 17643711 DOI: 10.1016/j.gie.2006.11.019]
52 **Lin HJ**, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. *Gastrointest Endosc* 2002; **55**: 615-619 [PMID: 11979239]
53 **Baettig B**, Haecki W, Lammer F, Jost R. Dieulafoy's disease: endoscopic treatment and follow up. *Gut* 1993; **34**: 1418-1421 [PMID: 8244112]
54 **Croffie J**, Somogyi L, Chuttani R, DiSario J, Liu J, Mishkin D, Shah RJ, Tierney W, Wong Kee Song LM, Petersen BT. Sclerosing agents for use in GI endoscopy. *Gastrointest Endosc* 2007; **66**: 1-6 [PMID: 17591465 DOI: 10.1016/j.gie.2007.02.014]
55 **Poddar U**, Thapa BR, Singh K. Endoscopic sclerotherapy in children: experience with 257 cases of extrahepatic portal venous obstruction. *Gastrointest Endosc* 2003; **57**: 683-686 [PMID: 12709697 DOI: 10.1067/mge.2003.194]
56 **Lo GH**, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001; **33**: 1060-1064 [PMID: 11343232 DOI: 10.1053/jhep.2001.24116]
57 **Rivet C**, Robles-Medranda C, Dumortier J, Le Gall C, Ponchon T, Lachaux A. Endoscopic treatment of gastroesophageal varices in young infants with cyanoacrylate glue: a pilot study. *Gastrointest Endosc* 2009; **69**: 1034-1038 [PMID: 19152910 DOI: 10.1016/j.gie.2008.07.025]
58 **Mitsunaga T**, Yoshida H, Kouchi K, Hishiki T, Saito T, Yamada S, Sato Y, Terui K, Nakata M, Takenouchi A, Ohnuma N. Pediatric gastroesophageal varices: treatment strategy and long-term results. *J Pediatr Surg* 2006; **41**: 1980-1983 [PMID: 17161186 DOI: 10.1016/j.jpedsurg.2006.08.022]
59 **Zargar SA**, Javid G, Khan BA, Yattoo GN, Shah AH, Gulzar GM, Singh J, Rehman BU, Din Z. Endoscopic ligation compared with sclerotherapy for bleeding esophageal varices in children with extrahepatic portal venous obstruction. *Hepatology* 2002; **36**: 666-672 [PMID: 12198659 DOI: 10.1053/jhep.2002.35278]
60 **Metz AJ**, Moss A, McLeod D, Tran K, Godfrey C, Chandra A, Bourke MJ. A blinded comparison of the safety and efficacy of hot biopsy forceps electrocauterization and conventional snare polypectomy for diminutive colonic polypectomy in a porcine model. *Gastrointest Endosc* 2013; **77**: 484-490 [PMID: 23199650 DOI: 10.1016/j.gie.2012.09.014]
61 **Isenberg G**, Sivak MV. Endoscopic hemostasis: something old, new, borrowed and now blue. *Gastrointest Endosc* 1998; **48**: 220-221 [PMID: 9717797]
62 **Khan K**, Schwarzenberg SJ, Sharp H, Weisdorf-Schindele S. Argon plasma coagulation: Clinical experience in pediatric patients. *Gastrointest Endosc* 2003; **57**: 110-112 [PMID: 12518146 DOI: 10.1067/mge.2003.13]
63 **Gauderer MW**, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872-875 [PMID: 6780678]
64 **Gauderer MW**. Percutaneous endoscopic gastrostomy and the evolution of contemporary long-term enteral access. *Clin Nutr* 2002; **21**: 103-110 [PMID: 12056781 DOI: 10.1054/clnu.2001.0533]
65 **Fortunato JE**, Troy AL, Cuffari C, Davis JE, Loza MJ, Oliva-

Hemker M, Schwarz KB. Outcome after percutaneous endoscopic gastrostomy in children and young adults. *J Pediatr Gastroenterol Nutr* 2010; **50**: 390-393 [PMID: 20179645 DOI: 10.1097/MPG.0b013e3181aed6f1]
66 **Eger R**, Reif S, Yaron A, Bojanover Y. [Percutaneous endoscopic gastrostomy (PEG) in children: indications, the procedure, outcomes, short and long-term complications]. *Harefuah* 2008; **147**: 21-24, 95 [PMID: 18300618]
67 **Sánchez-Ramírez CA**, Larrosa-Haro A, Vásquez Garibay EM, Larios-Arceo F. Caustic ingestion and oesophageal damage in children: Clinical spectrum and feeding practices. *J Paediatr Child Health* 2011; **47**: 378-380 [PMID: 21309879 DOI: 10.1111/j.1440-1754.2010.01984.x]
68 **Serhal L**, Gottrand F, Sfeir R, Guimber D, Devos P, Bonnevalle M, Storme L, Turck D, Michaud L. Anastomotic stricture after surgical repair of esophageal atresia: frequency, risk factors, and efficacy of esophageal bougie dilatations. *J Pediatr Surg* 2010; **45**: 1459-1462 [PMID: 20638524 DOI: 10.1016/j.jpedsurg.2009.11.002]
69 **Brown AK**, Tam PK. Measurement of gap length in esophageal atresia: a simple predictor of outcome. *J Am Coll Surg* 1996; **182**: 41-45 [PMID: 8542088]
70 **Koivusalo A**, Turunen P, Rintala RJ, van der Zee DC, Lindahl H, Bax NM. Is routine dilatation after repair of esophageal atresia with distal fistula better than dilatation when symptoms arise? Comparison of results of two European pediatric surgical centers. *J Pediatr Surg* 2004; **39**: 1643-1647 [PMID: 15547826]
71 **Temiz A**, Oguzkurt P, Ezer SS, Ince E, Hicsonmez A. Long-term management of corrosive esophageal stricture with balloon dilation in children. *Surg Endosc* 2010; **24**: 2287-2292 [PMID: 20177917 DOI: 10.1007/s00464-010-0953-x]
72 **Lan LC**, Wong KK, Lin SC, Sprigg A, Clarke S, Johnson PR, Tam PK. Endoscopic balloon dilatation of esophageal strictures in infants and children: 17 years' experience and a literature review. *J Pediatr Surg* 2003; **38**: 1712-1715 [PMID: 14666449]
73 **Abele JE**. The physics of esophageal dilatation. *Hepatogastroenterology* 1992; **39**: 486-489 [PMID: 1483657]
74 **Siersema PD**, de Wijkerslooth LR. Dilation of refractory benign esophageal strictures. *Gastrointest Endosc* 2009; **70**: 1000-1012 [PMID: 19879408 DOI: 10.1016/j.gie.2009.07.004]
75 **Said M**, Mekki M, Golli M, Memmi F, Hafsa C, Braham R, Belguith M, Letaief M, Gahbiche M, Nouri A, Ganouni A. Balloon dilatation of anastomotic strictures secondary to surgical repair of oesophageal atresia. *Br J Radiol* 2003; **76**: 26-31 [PMID: 12595322]
76 **Weintraub JL**, Eubig J. Balloon catheter dilatation of benign esophageal strictures in children. *J Vasc Interv Radiol* 2006; **17**: 831-835 [PMID: 16687749 DOI: 10.1097/01.rvi.0000217964.55623.19]
77 **Afzal NA**, Albert D, Thomas AL, Thomson M. A child with oesophageal strictures. *Lancet* 2002; **359**: 1032 [PMID: 11937184 DOI: 10.1016/s0140-6736(02)08095-9]
78 **Rosseneu S**, Afzal N, Yerushalmi B, Ibarguen-Secchia E, Lewindon P, Cameron D, Mahler T, Schwagten K, Köhler H, Lindley KJ, Thomson M. Topical application of mitomycin-C in oesophageal strictures. *J Pediatr Gastroenterol Nutr* 2007; **44**: 336-341 [PMID: 17325554 DOI: 10.1097/MPG.0b013e31802c6e45]
79 **Lang T**, Hümmer HP, Behrens R. Balloon dilation is preferable to bougienage in children with esophageal atresia. *Endoscopy* 2001; **33**: 329-335 [PMID: 11315894 DOI: 10.1055/s-2001-13691]
80 **Lakhdar-Idrissi M**, Khabbache K, Hida M. Esophageal endoscopic dilations. *J Pediatr Gastroenterol Nutr* 2012; **54**: 744-747 [PMID: 22270040 DOI: 10.1097/MPG.0b013e31824b16b2]
81 **Martin AJ**, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, Marley J. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002; **109**: 1061-1067 [PMID: 12042543]
82 **Kawahara H**, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. *Gastroenterology* 1997; **113**: 399-408 [PMID: 9247456]
83 **International Pediatric Endosurgery Group (IPEG)**. IPEG guidelines for the surgical treatment of pediatric gastroesophageal reflux disease (GERD). *J Laparoendosc Adv Surg Tech A* 2009; **19** Suppl 1: x-xiii [PMID: 19371153 DOI: 10.1089/lap.2009.9982.supp]
84 **Lightdale JR**, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics* 2013; **131**: e1684-e1695 [PMID: 23629618 DOI: 10.1542/peds.2013-0421]
85 **Roy-Shapira A**, Stein HJ, Scwartz D, Fich A, Sonnenschein E. Endoluminal methods of treating gastroesophageal reflux disease. *Dis Esophagus* 2002; **15**: 132-136 [PMID: 12220420]
86 **Swain CP**, Mills TN. An endoscopic sewing machine. *Gastrointest Endosc* 1986; **32**: 36-38 [PMID: 3512359]
87 **Tokudome K**, Funaki Y, Sasaki M, Izawa S, Tamura Y, Iida A, Ogasawara N, Konagaya T, Tokura Y, Kasugai K. Efficacy of endoluminal gastroplication in Japanese patients with proton pump inhibitor-resistant, non-erosive esophagitis. *World J Gastroenterol* 2012; **18**: 5940-5947 [PMID: 23139611 DOI: 10.3748/wjg.v18.i41.5940]
88 **Filipi CJ**, Lehman GA, Rothstein RI, Raijman I, Stiegmann GV, Waring JP, Hunter JG, Gostout CJ, Edmundowicz SA, Dunne DP, Watson PA, Cornet DA. Transoral, flexible endoscopic suturing for treatment of GERD: a multicenter trial. *Gastrointest Endosc* 2001; **53**: 416-422 [PMID: 11275879 DOI: 10.1067/mge.2001.113502]
89 **Mahmood Z**, Byrne PJ, McMahon BP, Murphy EM, Arfin Q, Ravi N, Weir DG, Reynolds JV. Comparison of transesophageal endoscopic plication (TEP) with laparoscopic Nissen fundoplication (LNF) in the treatment of uncomplicated reflux disease. *Am J Gastroenterol* 2006; **101**: 431-436 [PMID: 16542276 DOI: 10.1111/j.1572-0241.2006.00534.x]
90 **Velanovich V**, Ben-Menachem T, Goel S. Case-control comparison of endoscopic gastroplication with laparoscopic fundoplication in the management of gastroesophageal reflux disease: early symptomatic outcomes. *Surg Laparosc Endosc Percutan Tech* 2002; **12**: 219-223 [PMID: 12193813]
91 **Chadalavada R**, Lin E, Swafford V, Sedghi S, Smith CD. Comparative results of endoluminal gastroplasty and laparoscopic antireflux surgery for the treatment of GERD. *Surg Endosc* 2004; **18**: 261-265 [PMID: 14691698 DOI: 10.1007/s00464-003-8921-3]
92 **Thomson M**, Fritscher-Ravens A, Hall S, Afzal N, Ashwood P, Swain CP. Endoluminal gastroplication in children with significant gastro-oesophageal reflux disease. *Gut* 2004; **53**: 1745-1750 [PMID: 15542508 DOI: 10.1136/gut.2004.041921]
93 **Thomson M**, Antao B, Hall S, Afzal N, Hurlstone P, Swain CP, Fritscher-Ravens A. Medium-term outcome of endoluminal gastroplication with the EndoCinch device in children. *J Pediatr Gastroenterol Nutr* 2008; **46**: 172-177 [PMID: 18223376 DOI: 10.1097/MPG.0b013e31814d4de1]
94 **Ozawa S**, Kumai K, Higuchi K, Arakawa T, Kato M, Asaka M, Katada N, Kuwano H, Kitajima M. Short-term and long-term outcome of endoluminal gastroplication for the treatment of GERD: the first multicenter trial in Japan. *J Gastroenterol* 2009; **44**: 675-684 [PMID: 19440812 DOI: 10.1007/s00535-009-0064-4]
95 **Liao CC**, Lee CL, Lin BR, Bai CH, Hsieh YH, Wu CH, Gostout CJ. Endoluminal gastroplication for the treatment of gastroesophageal reflux disease: a 2-year prospective pilot study from Taiwan. *J Gastroenterol Hepatol* 2008; **23**: 398-405 [PMID: 18318824 DOI: 10.1111/j.1440-1746.2007.04906.x]
96 **Schiefke I**, Zabel-Langhennig A, Neumann S, Feisthammel J, Moessner J, Caca K. Long term failure of endoscopic gastroplication (EndoCinch). *Gut* 2005; **54**: 752-758 [PMID: 15888777 DOI: 10.1136/gut.2004.058354]
97 **Triadafilopoulos G**, DiBaise JK, Nostrant TT, Stollman NH, Anderson PK, Wolfe MM, Rothstein RI, Wo JM, Corley DA, Patti MG, Antignano LV, Goff JS, Edmundowicz SA, Castell DO, Rabine JC, Kim MS, Utley DS. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc* 2002; **55**: 149-156 [PMID: 11818914 DOI: 10.1067/mge.2002.121227]
98 **Utley DS**. The Stretta procedure: device, technique, and pre-clinical study data. *Gastrointest Endosc Clin N Am* 2003; **13**: 135-145 [PMID: 12797433]

99 **Perry KA**, Banerjee A, Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: 283-288 [PMID: 22874675 DOI: 10.1097/SLE.0b013e3182582e92]

100 **Corley DA**, Katz P, Wo JM, Stefan A, Patti M, Rothstein R, Edmundowicz S, Kline M, Mason R, Wolfe MM. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. *Gastroenterology* 2003; **125**: 668-676 [PMID: 12949712]

101 **Aziz AM**, El-Khayat HR, Sadek A, Mattar SG, McNulty G, Kongkam P, Guda MF, Lehman GA. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 818-825 [PMID: 19730952 DOI: 10.1007/s00464-009-0671-4]

102 **Islam S**, Geiger JD, Coran AG, Teitelbaum DH. Use of radiofrequency ablation of the lower esophageal sphincter to treat recurrent gastroesophageal reflux disease. *J Pediatr Surg* 2004; **39**: 282-286; discussion 282-286 [PMID: 15017538]

103 **Liu DC**, Somme S, Mavrelis PG, Hurwich D, Statter MB, Teitelbaum DH, Zimmermann BT, Jackson CC, Dye C. Stretta as the initial antireflux procedure in children. *J Pediatr Surg* 2005; **40**: 148-151; discussion 151-152 [PMID: 15868576 DOI: 10.1016/j.jpedsurg.2004.09.032]

104 **Bodmer WF**, Bailey CJ, Bodmer J, Bussey HJ, Ellis A, Gorman P, Lucibello FC, Murday VA, Rider SH, Scambler P. Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 1987; **328**: 614-616 [PMID: 3039373 DOI: 10.1038/328614a0]

105 **Hirata K**, Okazaki K, Nakayama Y, Nagata N, Itoh H, Ohsato K. Regression of gastric polyps in Gardner's syndrome with use of indomethacin suppositories: a case report. *Hepatogastroenterology* 1997; **44**: 918-920 [PMID: 9222715]

106 **Watanabe H**, Enjoji M, Yao T, Ohsato K. Gastric lesions in familial adenomatosis coli: their incidence and histologic analysis. *Hum Pathol* 1978; **9**: 269-283 [PMID: 26633]

107 **Attard TM**, Cuffari C, Tajouri T, Stoner JA, Eisenberg MT, Yardley JH, Abraham SC, Perry D, Vanderhoof J, Lynch H. Multicenter experience with upper gastrointestinal polyps in pediatric patients with familial adenomatous polyposis. *Am J Gastroenterol* 2004; **99**: 681-686 [PMID: 15089902 DOI: 10.1111/j.1572-0241.2004.04115.x]

108 **Attard TM**, Yardley JH, Cuffari C. Gastric polyps in pediatrics: an 18-year hospital-based analysis. *Am J Gastroenterol* 2002; **97**: 298-301 [PMID: 11866265 DOI: 10.1111/j.1572-0241.2002.05461.x]

109 **Domizio P**, Talbot IC, Spigelman AD, Williams CB, Phillips RK. Upper gastrointestinal pathology in familial adenomatous polyposis: results from a prospective study of 102 patients. *J Clin Pathol* 1990; **43**: 738-743 [PMID: 2170464]

110 **Dalla Valle R**, Zinicola R, Sianesi M, de'Angelis GL, Michiara M, Rasheed S, Phillips RK. Distal duodenal surveillance in familial adenomatous polyposis. *Dig Liver Dis* 2004; **36**: 559-560 [PMID: 15334781]

111 **Urs AN**, Martinelli M, Rao P, Thomson MA. Diagnostic and therapeutic utility of double-balloon enteroscopy in children. *J Pediatr Gastroenterol Nutr* 2014; **58**: 204-212 [PMID: 24126830 DOI: 10.1097/mpg.0000000000000192]

112 **Bizzarri B**, Borrelli O, de'Angelis N, Ghiselli A, Nervi G, Manfredi M, de'Angelis GL. Management of duodenal-jejunal polyps in children with peutz-jeghers syndrome with single-balloon enteroscopy. *J Pediatr Gastroenterol Nutr* 2014; **59**: 49-53 [PMID: 24590213 DOI: 10.1097/mpg.0000000000000351]

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REVIEW

Endoscopic management for congenital esophageal stenosis: A systematic review

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Abstract

Congenital esophageal stenosis (CES) is an extremely rare malformation, and standard treatment have not been completely established. By years of clinical research, evidence has been accumulated. We conducted systematic review to assess outcomes of the treatment for CES, especially the role of endoscopic modalities. A total of 144 literatures were screened and reviewed. CES was categorized in fibromuscular thickening, tracheobronchial remnants (TBR) and membranous web, and the frequency was 54%, 30% and 16%, respectively. Therapeutic option includes surgery and dilatation, and surgery tends to be reserved for ineffective dilatation. An essential point is that dilatation for TBR type of CES has low success rate and high rate of perforation. TBR can be distinguished by using endoscopic ultrasonography (EUS). Overall success rate of dilatation for CES with or without case selection by using EUS was 90% and 29%, respectively. Overall rate of perforation with or without case selection was 7% and 24%, respectively. By case selection using EUS, high success rate with low rate of perforation could be achieved. In conclusion, endoscopic dilatation has been established as a primary therapy for CES except TBR type. Repetitive dilatation with gradual step-up might be one of safe ways to minimize the risk of perforation.

Key words: Esophageal stenosis; Esophageal atresia; Tracheoesophageal fistula; Esophageal perforation; Dilatation; Endosonography; Deglutition disorders; Esophagoscopes; Esophageal ring; Plummer-Vinson syndrome

Core tip: Congenital esophageal stenosis (CES) is a rare malformation consisting of 3 types; fibromuscular thickening, tracheobronchial remnants (TBR) and membranous web. Endoscopic dilatation has been established as a primary therapy for CES except TBR type. Endoscopic ultrasonography is useful to distinguish TBR from other types of CES. Repetitive dilatation with gradual step-up is recommended to minimize the risk of perforation.

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INTRODUCTION

Congenital esophageal stenosis (CES) is an extremely rare malformation, and diagnostic criteria and standard treatment have not been completely established. By years of clinical research, evidence for the management of CES has been accumulated. In the management of CES, surgery and endoscopic modalities play a key role. Endoscopic management could be an effective and less-invasive, however, the risk of therapies and therapeutic margin should be considered. The aims of this systematic review were to identify all published studies of endoscopic management of CES and to assess outcomes in terms of relief of the stricture and complication rates. Frequency and characters of 3 categories of CES, and relationship with associated anomalies were also reviewed.

RESEARCH

A Definition of CES was based on the description by Nihoul-Fékété[1]; "an intrinsic stenosis of the esophagus, present although not necessarily symptomatic at birth, which is caused by congenital malformation of esophageal wall architecture".

Systematic review of English-language articles reporting CES was conducted by searching the PubMed database, in July 2014. Search terms "congenital" AND "esophageal stenosis" AND "endosc*", and MeSH term"Esophageal Stenosis" AND the term "congenital" were used. The references of each of the included studies were then screened for any additionally relevant articles. Studies were selected according to the following inclusion/exclusion criteria: the only inclusion criteria was diagnosis of CES, defined as intrinsic stenosis of the esophagus. Esophageal stricture due to compression by cardiac/vascular malformations or intrathoracic tumor was excluded, if it is "congenital". Secondary esophageal stenosis due to gastro-esophageal reflux, postoperative anastomotic stricture of esophageal atresia (EA) with/without tracheal fistula, leiomyoma and dermatological diseases including epidermolysis bullosa, dyskeratosis congenita, Rothmund Thomson syndrome and Goltz syndrome were also excluded. Review articles and mere letters were excluded. There were no exclusions based on patient numbers or length of follow-up. Accordingly, a total of 570 studies were identified by the initial searches, of which 144 studies satisfied the selection criteria (Figure 1). All the studies included were case reports or retrospective observational studies.

INCIDENCE

Investigators have commented on the rarity of CES, but the true incidence is still unknown. Bluestone *et al*[2] treated 24 cases of CES and approximately 200 cases of trachea-esophageal fistula in the single institution during the same 15 years, and estimated that the incidence of CES was one per 25000 births using that the incidence of tracheoesophageal fistula (TEF) was one per 2500 births[2]. Nihoul-Fékété *et al*[1] found 20 cases of CES and 484 cases of EA in the single institution during the same 25 years (1960-1984). According to this data, incidence of CES was lower than 1/20 of that of EA. Therefore, 1/25000-50000 live births is thought to be the incident rate of CES. These data are reliable and basically correct, but the frequency data should be revised based on the data at least in the 2000s.

CLASSIFICATION

The classification of CES has been confusing mainly because of its infrequency. Histological classification has been difficult because surgical specimens cannot be obtained if the only bougie can improves the symptom. Furthermore, it has also been difficult to differentiate CES from other non-congenital esophageal stricture such as achalasia, peptic esophageal stenosis due to gastroesophageal reflux and herpetic esophageal stenosis[3,4].

Various classification of CES had been proposed to date. Ohkawa *et al*[5] (1975) reported 5 entities of CES including tracheobronchial remnants, fibromuscular thickening, esophageal epithelioma, short esophagus and achalasia. Sneed *et al*[6] (1979) considered that there are congenital fibromuscular thickening (FMT), tracheobronchial remnants (TBR) and membranous web (MW) in the category of CES. Nihoul-Fékété (1989) clearly define CES and categorized the cases based on these 3 entities[1]. This categorization based on this sophisticated study has been broadly accepted to date. Ramesh *et al*[7] (2001) categorized CES into 3 groups; isolated segmental type, isolated diaphragm type and combined type. Isolated segmental type corresponds FMT and TBR, isolated diaphragm type corresponds MW and combined type corresponds segmental stenosis distal EA/TEF or MW. Although this classification involves the etiological consideration of CES, it is too complicated to use in clinical practice.

Frequency of 3 categories of CES were assessed by using the 3 observational studies including pediatric CES cases with detailed categorization (Table 1)[1,8,9]. Accordingly, overall frequency of FMT, TBR and MW were 53.8%, 29.9% and 16.2%, respectively. Locations of stenosis in each categories were assessed by using 52 case reports including 64 patients (Figure 2). Trends were as follows; MW mainly in the upper or middle third of the esophagus[10-27], FMT mainly in the

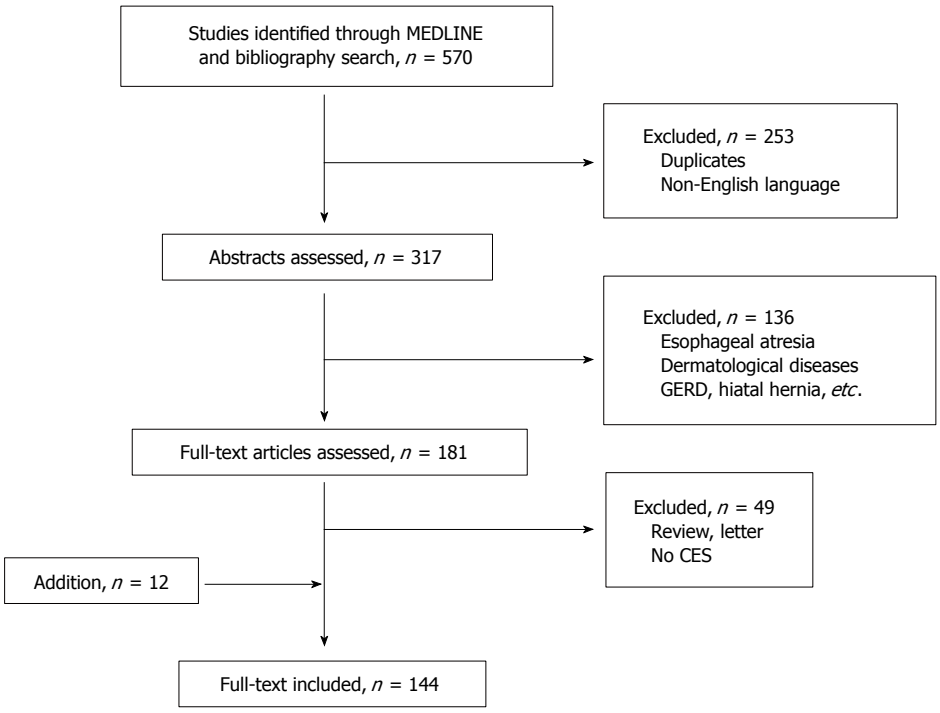

Figure 1 Flow chart of systematic search. CES: Congenital esophageal stenosis.

Table 1 Frequency of 3 categories of congenital esophageal stenosis

Ref.	FMT	TBR	MW	Total
Nihoul-Fékété *et asl*[1] (1987)	10 (50.0%)	4 (20.0%)	6 (30.0%)	20
Takamizawa *et al*[8] (2002)	13 (36.1%)	15 (41.7%)	8 (22.2%)[1]	36
Michaud *et al*[9] (2013)	40 (65.6%)	16 (26.2%)	5 (8.2%)	61
Total	63 (53.8%)	35 (29.9%)	19 (16.2%)	117

[1]Including cases of multiple web. FMT: Fibromuscular thickening; TBR: Tracheobronchial remnants; MW: Membranous web.

middle or lower third[28-39], and TBR mostly in the lower third[6,40-60].

Additionally, multiple web type of CES has been reported mainly in adults[61]. Only 1 pediatric case with multiple web has been reported[62].

ASSOCIATION WITH ESOPHAGEAL MALFORMATION

CES associated with esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) is not so rare, and 44 cases have been reported as case(s) report to date[12,22,26,28,31,33,37,44,47,50,55,63-75]. To assess relationship and EA and/or TEF, 14 observational studies of pediatric cases were reviewed[1,2,8,9,76-85]. According to the 4 observational studies[76,80,81,84], overall incidence rate of CES among patients with EA and/or TEF was 9.6% (Table 2). All the CES located in the middle to lower third of the esophagus; 13.5% in middle third of the esophagus, and 86.5% in lower third of the esophagus. Pathological findings of CES associated

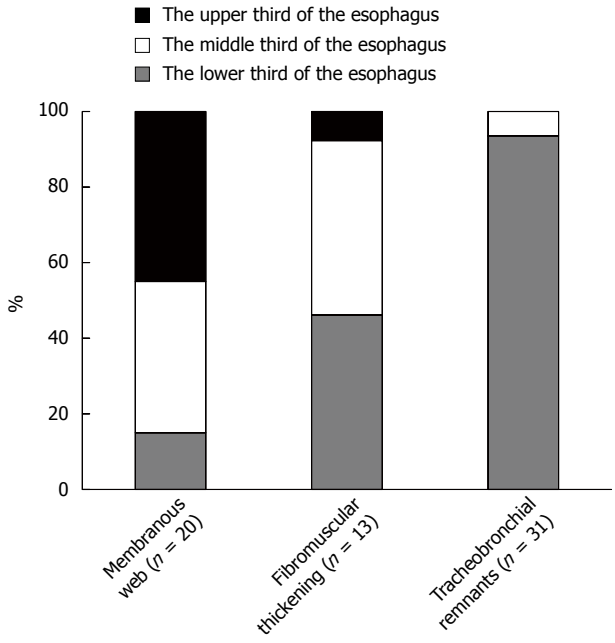

Figure 2 The locations of stenosis in each categories of congenital esophageal stenosis.

with TEF were not clear, because not all the cases had surgical specimens. In 15 cases (27% of CES cases), pathological assessment was performed; 10 cases (67%) had tracheobronchial remnant and 5 cases (33%) had fibromuscular stenosis. CES in TEF/EA is not a rare association, therefore, careful attention is required during the management of TEF/EA, especially in postoperative esophagogram.

According to the 10 observational studies[1,2,8,9,77-79,82,83,85],

Table 2 Incidence rate of congenital esophageal stenosis among patients with esophageal atresia and/or tracheoesophageal fistula

Ref.	Cases	Incidence rate	Location of CES	
			Middle	Lower
Holinger *et al*[76] (1963)	4/79	5.1%	0 (0%)	4 (100%)
Newman *et al*[80] (1997)	18/225	8.0%	NA	NA
Kawahara *et al*[81] (2001)	11/80	13.8%	2 (18%)	9 (82%)
Yoo *et al*[84] (2010)	22/187	11.8%	3 (14%)	19 (86%)
Total	55/571	9.6%	5 (13.5%)	32 (86.5%)

CES: Congenital esophageal stenosis.

overall incidence rate of EA and/or TEF among patients with CES was 24.8% (Table 3). Variation of the incident rate in each study may depend on study period, the role of institution and study design. Type of EA were not so different from original proportion; EA in 2.4%, EA+TEF in 92.7% and TEF in 4.9% of the cases. CES cases with complicated form of EA/TEF which cannot be classified were also reported[6,64].

Additionally, another esophageal malformation with CES, including esophageal duplication[22,50,86], diverticulum[18] and achalasia[11] were also reported.

ASSOCIATED ANOMALIES OTHER THAN ESOPHAGEAL MALFORMATION

Seven observational studies with detailed description about associated anomalies were reviewed[1,8,77-79,82,83]. These studies included a total of 199 cases of CES. The cases without any anomalies accounted for 55.3% of CES cases. Associated anomalies other than esophageal malformation were miscellaneous. Relatively frequent anomalies were as follows; congenital heart disease (4.5%), 21trisomy (4.0%), anorectal anomaly (2.0%), duodenal atresia (1.5%), tracheal malacia (1.5%), esophageal hiatal hernia (1.0%).

ADULT CASES

It is difficult to prove whether the adult cases with esophageal stenosis are truly "congenital". Actually, webs of the cervical esophagus have been commonly associated with Plummer-Vinson syndrome. In the largest series of adult CES cases, 62% of cases with upper esophageal webs had anemia, and all of them were female[87]. Khosla *et al*[88] also reported that among 117 patients with iron deficiency anemia, 6 cases (5.1%) had upper esophageal webs. Meanwhile, esophageal stenosis may also be found without the Plummer-Vinson syndrome. We found 24 case reports including 30 adult cases of CES with the categorization[10,11,13,15-18,20,21,40,41,59,89-99]. In these, 26 cases (86.7%) had MW type of CES[10,11,13,15-18,20,21,89-97,98,99]. In these, 16 cases had multiple webs[89-99], which was similar to ring of the trachea. Younes *et al*[61] treated 10 adult cases of multiple esophageal webs during 7 years, and stated that CES in adults is under-recognized cause for intermittent, long-standing dysphagia. Although extremely rare, TBR[40,41,59] and FMT[34] type of CES were also reported in adults.

FAMILY INCIDENCE

Occurrence of CES within a family was reported only in the 2 literatures; in father and son[94], and sisters[96]. They all were over middle age, suffered from dysphagia and/or food impaction for long duration, and had multiple esophageal webs (one of the sisters had no detail). In the former family, the son had male sibling who died 1 wk after birth because of an inability to swallow. In earlier reports, the nature of multiple esophageal webs has been speculated to be either congenital or acquired[89], and still remains unclear.

DIAGNOSIS

In diagnosis of CES, it is essential to exclude postnatally acquired stenoses (peptic, caustic, infectious, neoplastic), extrinsic compression, and achalasia[1]. Careful medical interview is of key importance. Both esophagogram and esophagoscopy is required to know location, range, form and degree of stenosis. To exclude peptic stenosis, pH monitoring may be useful. To exclude achalasia, measure of esophageal pressure is also informative.

Endoscopic ultrasonography (EUS) is brilliant way to classify the CES, especially distinguishing TBR from FMT[8,54,100,101]. By using this modality, the cartilage in the esophageal wall is visualized as low echoic area[54,100] or high echoic area[8,101]. Whether CES is classified as TBR or not is important information to determine the therapeutic strategy, because CES of TBR should be managed by surgery, not bougie due to high rate of perforation[55].

TREATMENT

Therapeutic option consists of dilatation and surgery. Although surgery tends to be reserved for ineffective dilatation, efficacy and risk of dilatation has been controversial. We, therefore, reviewed the literatures in which more than 5 cases of CES were treated by dilatation[1,8,9,79,81-83,85]. Studies were divided into two groups by whether EUS was used for case selection or not. EUS was to distinguish TBR type of CES. Accordingly, overall success rate of dilatation for CES with or without case selection was 89.7% and 28.9%, respectively (Table 4). Overall rate of perforation with or without case selection was 7.4% and 23.9%, respectively (Table 5). By using EUS, high success rate with low rate of perforation could be achieved. On the basis of this knowledge, flow chart of treatment is shown in Figure 3.

As a technique of dilatation, there are tapered

Table 3 Incidence rate of esophageal atresia and/or tracheoesophageal fistula among patients with congenital esophageal stenosis

Ref.	Cases	Incidence rate	EA	EA + TEF	TEF
Bluestone *et al*[2] (1969)	0/24	0.0%	0	0	0
Nishina *et al*[77] (1981)	4/81	4.9%	0	3	1
Dominguez *et al*[78] (1985)	5/34	14.7%	0	5	0
Nihoul-Fékété *et al*[1] (1987)	2/20	10.0%	0	1	1
Yeung *et al*[79] (1992)	6/8	75.0%	1	4	1
Vasudevan *et al*[82] (2002)	4/6	66.7%	1	2	1
Takamizawa *et al*[8] (2002)	13/36	36.1%	0	13	0
Amae *et al*[83] (2003)	4/14	28.6%	0	4	0
Romeo *et al*[85] (2011)	15/47	31.9%	0	15	0
Michaud *et al*[9] (2013)	29/61	47.5%	0	29	0
Total	82/331	24.8%	2 (2.4%)	76 (92.7%)	4 (4.9%)

EA: Esophageal atresia; TEF: Tracheoesophageal fistula.

Table 4 Success rate of dilatation for congenital esophageal stenosis with/without case selection by endoscopic ultrasonography

Ref.	Case selection by EUS		Modality
	+	-	
	Success rate		
Takamizawa *et al*[8] (2002)	16/21 (76.2%)	-	BD
Romeo *et al*[85] (2011)	45/47 (95.7%)	-	BD
Nihoul-Fékété *et al*[1] (1987)	-	7/14 (50.0%)	BD or TD
Yeung *et al*[79] (1992)	-	0/7 (0.0%)	BD or TD
Kawahara *et al*[81] (2001)	-	2/9 (22.2%)	BD
Vasudevan *et al*[82] (2002)	-	3/7 (42.9%)	TD
Amae *et al*[83] (2003)	-	3/11 (27.3%)	BD or TD
Michaud *et al*[9] (2013)	-	13/49 (26.5%)	BD or TD
Total	611/68 (89.7%)	28/97 (28.9%)	

BD: Balloon dilatator; TD: Tapered dilator; EUS: Endoscopic ultrasonography.

Table 5 Rate of perforation during dilatation of congenital esophageal stenosis

Ref.	Case selection by EUS		Modality
	+	-	
	Rate of perforation		
Takamizawa *et al*[8] (2002)	0/21 (0.0%)	-	BD
Romeo *et al*[85] (2011)	15/47 (10.6%)	-	BD
Nihoul-Fékété *et al*[1] (1987)	-	6/14 (42.9%)	BD or TD
Yeung *et al*[79] (1992)	-	1/7 (14.3%)	BD or TD
Newman *et al*[80] (1997)		3/18 (16.7%)	BD
Kawahara *et al*[81] (2001)	-	4/9 (44.4%)	BD
Amae *et al*[83] (2003)	-	1/11 (9.1%)	BD or TD
Fan *et al*[104] (2011)	-	1/8 (12.5%)	BD
Total	5/68 (7.4%)	16/67 (23.9%)	

BD: Balloon dilatator; TD: Tapered dilator; EUS: Endoscopic ultrasonography.

dilator and balloon dilatator, but there has been no comparison study of these. Some prefer balloon dilator because it enable expanding force to focus on the stenotic segment without shear stress, resulting in more effective and safer[8,102]. Appropriate diameter of dilatation for CES is still unknown. Kozarek *et al*[103] suggested that inflation of a single large-diameter dilator of less than 15 mm or an incremental dilation of more than 3 mm may be safe in simple esophageal strictures in adults. Fan *et al*[104] reported 9 procedures of balloon dilatation for CES including 1 esophageal perforation. Although there was no statistical significance, mean balloon diameter of the procedure with/without perforation was 12.1 mm and 15.0 mm, respectively. Mean dilation achieved with/without perforation was 5.4 mm and 8.4 mm, respectively. Not surprisingly, large dilatation with large increment might be a risk of perforation. Therefore, repetitive dilatation with gradual step-up might be one of safe ways to minimize the risk of perforation.

In cases of MW type of CES, efficacy of endoscopic dilatation with radial incision of the web has been reported. Instruments for incision include electrocoagulation[17,19,105], high-frequency-wave[27] and laser[23]. Nose *et al*[27] used balloon catheter for pulling up the web from the distal side during incision. Adverse events during dilatation with incision have not been reported.

LONG-TERM PROGNOSIS

It is well known that the association of Plummer-Vinson syndrome with carcinoma of the mouth, hypopharynx and upper esophagus. In the 58 adult cases of MW type of CES, 9 cases (15.5%) had carcinoma; buccal carcinoma in 6, esophageal carcinoma in 3[88]. Other than MW type, only one case has been reported, who had esophageal carcinoma associated with FMT type of CES; 65-year-old man who had suffered from dysphagia and vomiting since birth, but had not received any treatment because of mild symptom, underwent esophagectomy for worsening symptom. The resected specimen revealed squamous cell carcinoma in the region of fibromuscular stenosis[34]. The authors speculated that chronic mechanical stimulation by food trapped above the stenosis may have induced dysplasia of the mucosa. Special attention should be paid to status of the esophageal passage. Long-term functional prognosis after dilatation of pediatric CES has not been reported. Further studies are still needed.

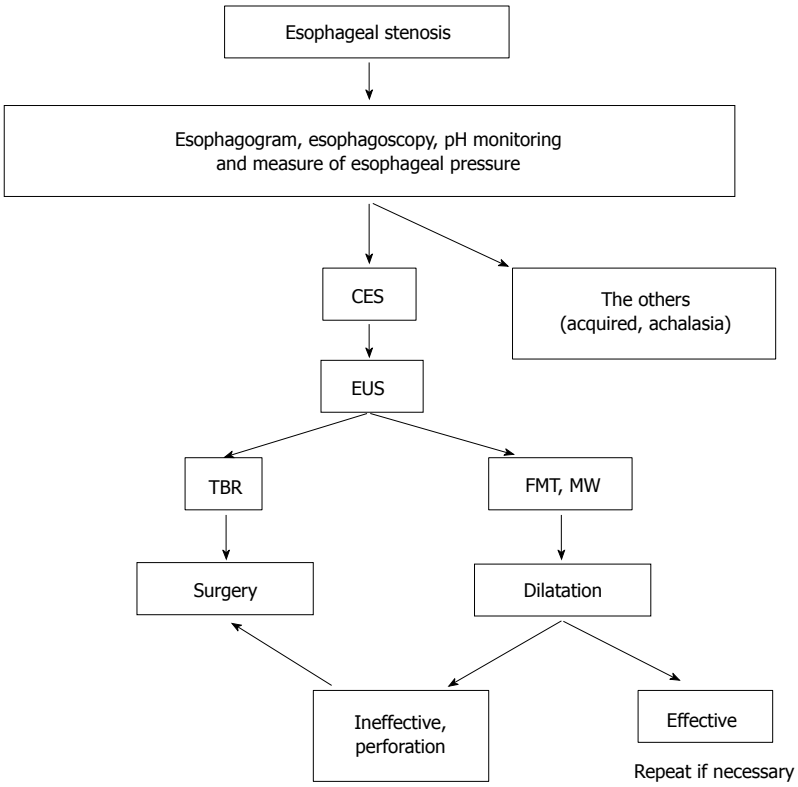

Figure 3 Flow chart of diagnosis and treatment for congenital esophageal stenosis.

CONCLUSION

Endoscopic dilatation has been established as a primary therapy for CES except TBR type. EUS is useful to distinguish TBR from other types of CES. Repetitive dilatation with gradual step-up is recommended to minimize the risk of perforation.

REFERENCES

1 **Nihoul-Fékété C**, De Backer A, Lortat-Jacob S, Pellerin D. Congenital esophageal stenosis. A review of 20 cases. *Pediatr Surg Int* 1987; **2**: 86-92 [DOI: 10.1007/BF00174179]

2 **Bluestone CD**, Kerry R, Sieber WK. Congenital esophageal stenosis. *Laryngoscope* 1969; **79**: 1095-1103 [PMID: 5786187 DOI: 10.1288/00005537-196906000-00004]

3 **Valerio D**, Jones PF, Stewart AM. Congenital oesophageal stenosis. *Arch Dis Child* 1977; **52**: 414-416 [PMID: 869573 DOI: 10.1136/adc.52.5.414]

4 **Rossier A**, de Montis G, Chabrolle JP. Congenital oesophageal stenosis and herpes simplex infection. *Arch Dis Child* 1977; **52**: 982 [PMID: 606180 DOI: 10.1136/adc.52.12.982]

5 **Ohkawa H**, Takahashi H, Hoshino Y, Sato H. Lower esophageal stenosis in association with tracheobronchial remnants. *J Pediatr Surg* 1975; **10**: 453-457 [PMID: 1151581 DOI: 10.1016/0022-3468(75)90184-0]

6 **Sneed WF**, LaGarde DC, Kogutt MS, Arensman RM. Esophageal stenosis due to cartilaginous tracheobronchial remnants. *J Pediatr Surg* 1979; **14**: 786-788 [PMID: 551158 DOI: 10.1016/S0022-3468(79)80265-1]

7 **Ramesh JC**, Ramanujam TM, Jayaram G. Congenital esophageal stenosis: report of three cases, literature review, and a proposed classification. *Pediatr Surg Int* 2001; **17**: 188-192 [PMID: 11315285 DOI: 10.1007/s003830000458]

8 **Takamizawa S**, Tsugawa C, Mouri N, Satoh S, Kanegawa K, Nishijima E, Muraji T. Congenital esophageal stenosis: Therapeutic strategy based on etiology. *J Pediatr Surg* 2002; **37**: 197-201 [PMID: 11819198 DOI: 10.1053/jpsu.2002.30254]

9 **Michaud L**, Coutenier F, Podevin G, Bonnard A, Becmeur F, Khen-Dunlop N, Auber F, Maurel A, Gelas T, Dassonville M, Borderon C, Dabadie A, Weil D, Piolat C, Breton A, Djeddi D, Morali A, Bastiani F, Lamireau T, Gottrand F. Characteristics and management of congenital esophageal stenosis: findings from a multicenter study. *Orphanet J Rare Dis* 2013; **8**: 186 [PMID: 24289834]

10 **Adler RH**. Congenital esophageal webs. *J Thorac Cardiovasc Surg* 1963; **45**: 175-185 [PMID: 14011099]

11 **Salzman AJ**. Lower esophageal WEB asssociated with achalasia of the esophagus. *N Y State J Med* 1965; **65**: 1922-1925 [PMID: 14338465]

12 **Azimi F**, O'Hara AE. Congenital intraluminal mucosal web of the esophagus with tracheo-esophageal fistula. *Am J Dis Child* 1973; **125**: 92-95 [PMID: 4683963]

13 **Liebman WM**, Samloff IM. Congenital membranous stenosis of the midesophagus. A case report and literature survey. *Clin Pediatr (Phila)* 1973; **12**: 660-662 [PMID: 4202409]

14 **Gilat T**, Rozen P. Fiberoptic endoscopic diagnosis and treatment of a congenital esophageal diaphragm. *Am J Dig Dis* 1975; **20**: 781-785 [PMID: 1155417 DOI: 10.1007/BF01070837]

15 **Ikard RW**, Rosen HE. Midesophageal web in adults. *Ann Thorac Surg* 1977; **24**: 355-358 [PMID: 907403]

16 **Shauffer IA**, Phillips HE, Sequeira J. The jet phenomenon: a manifestation of esophageal web. *AJR Am J Roentgenol* 1977; **129**: 747-748 [PMID: 409259]

17 **Acosta JC**. Congenital stenosis of the esophagus. *Gastrointest Endosc* 1981; **27**: 197-198 [PMID: 7297835]

18 **Mercer CD**, Hill LD. Esophageal web associated with Zenker's diverticulum: a possible cause of continuing dysphagia after diverticulectomy. *Can J Surg* 1985; **28**: 375-376 [PMID: 3926291]

19 **Mares AJ**, Bar-Ziv J, Lieberman A, Tovi F. Congenital esophageal stenosis. Transendoscopic web incision. *J Clin Gastroenterol* 1986;

8: 555-558 [PMID: 3782754]
20 **Shergill IS**, Khanna S, Kaur J. Congenital upper esophageal web. *Indian J Chest Dis Allied Sci* 1986; **28**: 156-159 [PMID: 3596668]
21 **Beggs D**, Morgan WE. Spontaneous perforation of cervical oesophagus associated with oesophageal web. *J Laryngol Otol* 1989; **103**: 537-538 [PMID: 2754327]
22 **Snyder CL**, Bickler SW, Gittes GK, Ramachandran V, Ashcraft KW. Esophageal duplication cyst with esophageal web and tracheoesophageal fistula. *J Pediatr Surg* 1996; **31**: 968-969 [PMID: 8811570 DOI: 10.1016/S0022-3468(96)90424-8]
23 **Roy GT**, Cohen RC, Williams SJ. Endoscopic laser division of an esophageal web in a child. *J Pediatr Surg* 1996; **31**: 439-440 [PMID: 8708922 DOI: 10.1016/S0022-3468(96)90757-5]
24 **Grabowski ST**, Andrews DA. Upper esophageal stenosis: two case reports. *J Pediatr Surg* 1996; **31**: 1438-1439 [PMID: 8906683 DOI: 10.1016/S0022-3468(96)90850-7]
25 **Kumuro H**, Makino S, Tsuchiya I, Shibusawa H, Kusaka T, Nishi A. Cervical esophageal web in a 13-year-old boy with growth failure. *Pediatr Int* 1999; **41**: 568-570 [PMID: 10530075 DOI: 10.1046/j.1442-200X.1999.01107.x]
26 **Nagae I**, Tsuchida A, Tanabe Y, Takahashi S, Minato S, Aoki T. High-grade congenital esophageal stenosis owing to a membranous diaphragm with tracheoesophageal fistula. *J Pediatr Surg* 2005; **40**: e11-e13 [PMID: 16226967 DOI: 10.1016/j.jpedsurg.2005.06.030]
27 **Nose S**, Kubota A, Kawahara H, Okuyama H, Oue T, Tazuke Y, Ihara Y, Okada A. Endoscopic membranectomy with a high-frequency-wave snare/cutter for membranous stenosis in the upper gastrointestinal tract. *J Pediatr Surg* 2005; **40**: 1486-1488 [PMID: 16150355 DOI: 10.1016/j.jpedsurg.2005.05.053]
28 **Tuqan NA**. Annular stricture of the esophagus distal to congenital tracheoesophageal fistula. *Surgery* 1962; **52**: 394-395 [PMID: 13923110]
29 **Takayanagi K**, Ii K, Komi N. Congenital esophageal stenosis with lack of the submucosa. *J Pediatr Surg* 1975; **10**: 425-426 [PMID: 1142055]
30 **Groote AD**, Laurini RN, Polman HA. A case of congenital esophageal stenosis. *Hum Pathol* 1985; **16**: 1170-1171 [PMID: 4054897 DOI: 10.1016/S0046-8177(85)80189-1]
31 **Homnick DN**. H-type tracheoesophageal fistula and congenital esophageal stenosis. *Chest* 1993; **103**: 308-309 [PMID: 8417914]
32 **Garau P**, Orenstein SR. Congenital esophageal stenosis treated by balloon dilation. *J Pediatr Gastroenterol Nutr* 1993; **16**: 98-101 [PMID: 8433248]
33 **Pesce C**, Musi L, Campobasso P, Costa L, Mercurella A. Conservative non-surgical management of congenital oesophageal stenosis associated with oesophageal atresia. *Ital J Gastroenterol Hepatol* 1999; **31**: 899-900 [PMID: 10670002]
34 **Tabira Y**, Yasunaga M, Sakaguchi T, Okuma T, Yamaguchi Y, Kuhara H, Honda Y, Iyama K, Kawasuji M. Adult case of squamous cell carcinoma arising on congenital esophageal stenosis due to fibromuscular hypertrophy. *Dis Esophagus* 2002; **15**: 336-339 [PMID: 12472484 DOI: 10.1046/j.1442-2050.2002.00270.x]
35 **Setty SP**, Harrison MW. Congenital esophageal stenosis: a case report and review of the literature. *Eur J Pediatr Surg* 2004; **14**: 283-286 [PMID: 15343471 DOI: 10.1055/s-2004-817943]
36 **Machmouchi MA**, Al Harbi M, Bakhsh KA, Al Shareef ZH. Congenital esophageal stenosis. *Saudi Med J* 2004; **25**: 648-650 [PMID: 15138535]
37 **Queizán A**, Martínez L. Congenital segmental fibromuscular hypertrophy of the esophagus and esophageal atresia: an uncommon case. *Eur J Pediatr Surg* 2006; **16**: 201-204 [PMID: 16909361 DOI: 10.1055/s-2005-873075]
38 **Martinez-Ferro M**, Rubio M, Piaggio L, Laje P. Thoracoscopic approach for congenital esophageal stenosis. *J Pediatr Surg* 2006; **41**: E5-E7 [PMID: 17011258 DOI: 10.1016/j.jpedsurg.2006.06.022]
39 **Al-Tokhais TI**, Ahmed AM, Aljubab AS. Congenital esophageal stenosis and antral web. A new association and management challenge. *Saudi Med J* 2010; **31**: 1166-1168 [PMID: 20953536]
40 Case records of the Massachusetts General Hospital; case 42411. *N Engl J Med* 1956; **255**: 707-710 [PMID: 13369703 DOI: 10.1056/NEJM195610112551508]
41 **Bergmann M**, charnas RM. Tracheobronchial rests in the esophagus; their relation to some benign strictures and certain types of cancer of the esophagus. *J Thorac Surg* 1958; **35**: 97-104 [PMID: 13514806]
42 **Paulino F**, Roselli A, Aprigliano F. Congenital esophageal stricture due to tracheobraonchial remnants. *Surgery* 1963; **53**: 547-550 [PMID: 13941996]
43 **Ishida M**, Tsuchida Y, Saito S, Tsunoda A. Congenital esophageal stenosis due to tracheobronchial remnants. *J Pediatr Surg* 1969; **4**: 339-345 [PMID: 5788952]
44 **Spitz L**. Congenital esophageal stenosis distal to associated esophageal atresia. *J Pediatr Surg* 1973; **8**: 973-974 [PMID: 4785583]
45 **Marcus PB**, de Wet Lubbe JJ, Muller Botha GS. An unusual cause of congenital oesophageal stenosis. *S Afr J Surg* 1973; **11**: 145-146 [PMID: 4771592]
46 **Anderson LS**, Shackelford GD, Mancilla-Jimenez R, McAlister WH. Cartilaginous esophageal ring: a cause of esophageal stenosis in infants and children. *Radiology* 1973; **108**: 665-666 [PMID: 4198827]
47 **Deiraniya AK**. Congenital oesophageal stenosis due to tracheobronchial remnants. *Thorax* 1974; **29**: 720-725 [PMID: 4450182]
48 **Rose JS**, Kassner EG, Jurgens KH, Farman J. Congenital oesophageal strictures due to cartilaginous rings. *Br J Radiol* 1975; **48**: 16-18 [PMID: 1109621]
49 **Briceño LI**, Grases PJ, Gallego S. Tracheobronchial and pancreatic remnants causing esophageal stenosis. *J Pediatr Surg* 1981; **16**: 731-732 [PMID: 7310610]
50 **Ibrahim NB**, Sandry RJ. Congenital oesophageal stenosis caused by tracheobronchial structures in the oesophageal wall. *Thorax* 1981; **36**: 465-468 [PMID: 7314018]
51 **Bar-Maor JA**, Posen JA, Hamilton DG, Chappell JS. Congenital oesophageal stenosis due to cartilaginous tracheobronchial remnants. *S Afr J Surg* 1983; **21**: 43-47 [PMID: 6879351]
52 **Shoshany G**, Bar-Maor JA. Congenital stenosis of the esophagus due to tracheobronchial remnants: a missed diagnosis. *J Pediatr Gastroenterol Nutr* 1986; **5**: 977-979 [PMID: 3794920]
53 **Olguner M**, Ozdemir T, Akgür FM, Aktuğ T. Congenital esophageal stenosis owing to tracheobronchial remnants: a case report. *J Pediatr Surg* 1997; **32**: 1485-1487 [PMID: 9349777 DOI: 10.1016/S0022-3468(97)90570-4]
54 **Kouchi K**, Yoshida H, Matsunaga T, Ohtsuka Y, Nagatake E, Satoh Y, Terui K, Mitsunaga T, Ochiai T, Arima M, Ohnuma N. Endosonographic evaluation in two children with esophageal stenosis. *J Pediatr Surg* 2002; **37**: 934-936 [PMID: 12037771 DOI: 10.1053/jpsu.2002.32921]
55 **Zhao LL**, Hsieh WS, Hsu WM. Congenital esophageal stenosis owing to ectopic tracheobronchial remnants. *J Pediatr Surg* 2004; **39**: 1183-1187 [PMID: 15300523 DOI: 10.1016/j.jpedsurg.2004.04.039]
56 **Maeda K**, Hisamatsu C, Hasegawa T, Tanaka H, Okita Y. Circular myectomy for the treatment of congenital esophageal stenosis owing to tracheobronchial remnant. *J Pediatr Surg* 2004; **39**: 1765-1768 [PMID: 15616923 DOI: 10.1016/j.jpedsurg.2004.08.016]
57 **Saito T**, Ise K, Kawahara Y, Yamashita M, Shimizu H, Suzuki H, Gotoh M. Congenital esophageal stenosis because of tracheobronchial remnant and treated by circular myectomy: a case report. *J Pediatr Surg* 2008; **43**: 583-585 [PMID: 18358309 DOI: 10.1016/j.jpedsurg.2007.11.017]
58 **Deshpande AV**, Shun A. Laparoscopic treatment of esophageal stenosis due to tracheobronchial remnant in a child. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 107-109 [PMID: 18976145 DOI: 10.1089/lap.2008.0070]
59 **Longcroft-Wheaton G**, Ellis R, Somers S. Dysphagia in a 30-year-old woman: too old for a congenital abnormality? *Br J Hosp Med (Lond)* 2010; **71**: 170-171 [PMID: 20220726]
60 **Quiros JA**, Hirose S, Patino M, Lee H. Esophageal tracheobronchial remnant, endoscopic ultrasound diagnosis, and

surgical management. *J Pediatr Gastroenterol Nutr* 2013; **56**: e14 [PMID: 22925920 DOI: 10.1097/MPG.0b013e31826a9086]
61 **Younes Z**, Johnson DA. Congenital esophageal stenosis: clinical and endoscopic features in adults. *Dig Dis* 1999; **17**: 172-177 [PMID: 10697666]
62 **Carlisle WR**. A case of multiple esophageal webs and rings. *Gastrointest Endosc* 1984; **30**: 184-185 [PMID: 6735096]
63 **Goldenberg IS**. An unusual variation of congenital tracheo-esophageal fistula. *J Thorac cardiovasc Surg* 1960; **40**: 114-116
64 **Lister J**. An unusual variation of oesophageal atresia. *Arch Dis Child* 1963; **38**: 176-179 [PMID: 13930938 DOI: 10.1136/adc.38.198.176]
65 **Stephens HB**. H-type tracheoesophageal fistula complicated by esophageal stenosis. *J Thorac Cardiovasc Surg* 1970; **59**: 325-329 [PMID: 5415076]
66 **Mahour GH**, Johnston PW, Gwinn JL, Hays DM. Congenital esophageal stenosis distal to esophageal atresia. *Surgery* 1971; **69**: 936-939 [PMID: 5578456]
67 **Jewsbury P**. An unusual case of congenital oesophageal stricture. *Br J Surg* 1971; **58**: 475-476 [PMID: 5089629]
68 **Mortensson W**. Congenital oesophageal stenosis distal to oesophageal atresia. *Pediatr Radiol* 1975; **3**: 149-151 [PMID: 1233429]
69 **Sheridan J**, Hyde I. Oesophageal stenosis distal to oesophageal atresia. *Clin Radiol* 1990; **42**: 274-276 [PMID: 2225734]
70 **Neilson IR**, Croitoru DP, Guttman FM, Youssef S, Laberge JM. Distal congenital esophageal stenosis associated with esophageal atresia. *J Pediatr Surg* 1991; **26**: 478-481; discussion 481-482 [PMID: 2056411 DOI: 10.1016/0022-3468(91)90999-A]
71 **Shorter NA**, Mooney DP, Vaccaro TJ, Sargent SK. Hydrostatic balloon dilation of congenital esophageal stenoses associated with esophageal atresia. *J Pediatr Surg* 2000; **35**: 1742-1745 [PMID: 11101727 DOI: 10.1053/jpsu.2000.19238]
72 **Babu R**, Hutton KA, Spitz L. H-type tracheo-oesophageal fistula with congenital oesophageal stenosis. *Pediatr Surg Int* 2005; **21**: 386-387 [PMID: 15609054 DOI: 10.1007/s00383-004-1343-z]
73 **Jones DW**, Kunisaki SM, Teitelbaum DH, Spigland NA, Coran AG. Congenital esophageal stenosis: the differential diagnosis and management. *Pediatr Surg Int* 2010; **26**: 547-551 [PMID: 20405275 DOI: 10.1007/s00383-010-2568-7]
74 **van Poll D**, van der Zee DC. Thoracoscopic treatment of congenital esophageal stenosis in combination with H-type tracheoesophageal fistula. *J Pediatr Surg* 2012; **47**: 1611-1613 [PMID: 22901927 DOI: 10.1016/j.jpedsurg.2012.05.015]
75 **Escobar MA**, Pickens MK, Holland RM, Caty MG. Oesophageal atresia associated with congenital oesophageal stenosis. *BMJ Case Rep* 2013; **2013**: [PMID: 23696146 DOI: 10.1136/bcr-2013-009620]
76 **Holinger PH**, Johnston KC. Postsurgical endoscopid problems of congenital esophageal atresia. *Ann Otol Rhinol Laryngol* 1963; **72**: 1035-1049 [PMID: 14088721]
77 **Nishina T**, Tsuchida Y, Saito S. Congenital esophageal stenosis due to tracheobronchial remnants and its associated anomalies. *J Pediatr Surg* 1981; **16**: 190-193 [PMID: 7241323]
78 **Dominguez R**, Zarabi M, Oh KS, Bender TM, Girdany BR. Congenital oesophageal stenosis. *Clin Radiol* 1985; **36**: 263-266 [PMID: 4064508]
79 **Yeung CK**, Spitz L, Brereton RJ, Kiely EM, Leake J. Congenital esophageal stenosis due to tracheobronchial remnants: a rare but important association with esophageal atresia. *J Pediatr Surg* 1992; **27**: 852-855 [PMID: 1640332 DOI: 10.1016/0022-3468(92)90382-H]
80 **Newman B**, Bender TM. Esophageal atresia/tracheoesophageal fistula and associated congenital esophageal stenosis. *Pediatr Radiol* 1997; **27**: 530-534 [PMID: 9174027 DOI: 10.1007/s002470050174]
81 **Kawahara H**, Imura K, Yagi M, Kubota A. Clinical characteristics of congenital esophageal stenosis distal to associated esophageal atresia. *Surgery* 2001; **129**: 29-38 [PMID: 11150031 DOI: 10.1067/msy.2001.109064]
82 **Vasudevan SA**, Kerendi F, Lee H, Ricketts RR. Management of congenital esophageal stenosis. *J Pediatr Surg* 2002; **37**: 1024-1026 [PMID: 12077763 DOI: 10.1053/jpsu.2002.33834]
83 **Amae S**, Nio M, Kamiyama T, Ishii T, Yoshida S, Hayashi Y, Ohi R. Clinical characteristics and management of congenital esophageal stenosis: a report on 14 cases. *J Pediatr Surg* 2003; **38**: 565-570 [PMID: 12677567 DOI: 10.1053/jpsu.2003.50123]
84 **Yoo HJ**, Kim WS, Cheon JE, Yoo SY, Park KW, Jung SE, Shin SM, Kim IO, Yeon KM. Congenital esophageal stenosis associated with esophageal atresia/tracheoesophageal fistula: clinical and radiologic features. *Pediatr Radiol* 2010; **40**: 1353-1359 [PMID: 20221592 DOI: 10.1007/s00247-010-1603-0]
85 **Romeo E**, Foschia F, de Angelis P, Caldaro T, Federici di Abriola G, Gambitta R, Buoni S, Torroni F, Pardi V, Dall'oglio L. Endoscopic management of congenital esophageal stenosis. *J Pediatr Surg* 2011; **46**: 838-841 [PMID: 21616237 DOI: 10.1016/j.jpedsurg.2011.02.010]
86 **Fuchs J**, Grasshoff S, Schirg E, Glüer S, Bürger D. Tubular esophageal duplication associated with esophageal stenosis, pericardial aplasia, diaphragmatic hernia, ramification anomaly of lower lobe bronchus and partial pancreas anulare. *Eur J Pediatr Surg* 1998; **8**: 102-104 [PMID: 9617611 DOI: 10.1055/s-2008-1071132]
87 **Shamma'a MH**, Benedict EB. Esophageal webs; a report of 58 cases & an attempt at classification. *N Engl J Med* 1958; **259**: 378-384 [PMID: 13566486 DOI: 10.1056/NEJM195808212590805]
88 **Khosla SN**. Cricoid webs--incidence and follow-up study in Indian patients. *Postgrad Med J* 1984; **60**: 346-348 [PMID: 6739392 DOI: 10.1136/pgmj.60.703.346]
89 **Shiflett DW**, Gilliam JH, Wu WC, Austin WE, Ott DJ. Multiple esophageal webs. *Gastroenterology* 1979; **77**: 556-559 [PMID: 456849]
90 **Longstreth GF**, Wolochow DA, Tu RT. Double congenital midesophageal webs in adults. *Dig Dis Sci* 1979; **24**: 162-165 [PMID: 428304]
91 **Janisch HD**, Eckardt VF. Histological abnormalities in patients with multiple esophageal webs. *Dig Dis Sci* 1982; **27**: 503-506 [PMID: 7083985]
92 **Munitz HA**, Ott DJ, Rocamora LR, Wu WC. Multiple webs of the esophagus. *South Med J* 1983; **76**: 405-406 [PMID: 6828912]
93 **Agarwal VP**, Marcel BR. Multiple esophageal rings. *Gastrointest Endosc* 1990; **36**: 147-149 [PMID: 2335284]
94 **Harrison CA**, Katon RM. Familial multiple congenital esophageal rings: report of an affected father and son. *Am J Gastroenterol* 1992; **87**: 1813-1815 [PMID: 1449148]
95 **Pokieser P**, Schima W, Schober E, Böhm P, Stacher G, Levine MS. Congenital esophageal stenosis in a 21-year-old man: clinical and radiographic findings. *AJR Am J Roentgenol* 1998; **170**: 147-148 [PMID: 9423621]
96 **Rangel R**, Lizarzabal M. Familial multiple congenital esophageal rings. *Dig Dis* 1998; **16**: 325 [PMID: 10223838]
97 **Bhaskar SK**, Bin-Sagheer S, Brady PG. Congenital esophageal stenosis. *Dig Dis* 2000; **18**: 186 [PMID: 11279339 DOI: 10.1159/000051394]
98 **Gonzalez JA**, Craft CM, Knight TT, Messerschmidt WH. Superimposed spontaneous esophageal perforation in congenital esophageal stenosis. *Ann Thorac Surg* 2004; **77**: 1098-1100 [PMID: 14992945 DOI: 10.1016/S0003-4975(03)00890-7]
99 **Smith MA**, Patterson GA, Cooper JD. Dysphagia in the young male: the ringed esophagus. *Ann Thorac Surg* 2006; **81**: 354-356 [PMID: 16368405 DOI: 10.1016/j.athoracsur.2004.10.063]
100 **Bocus P**, Realdon S, Eloubeidi MA, Diamantis G, Betalli P, Gamba P, Zanon GF, Battaglia G. High-frequency miniprobes and 3-dimensional EUS for preoperative evaluation of the etiology of congenital esophageal stenosis in children (with video). *Gastrointest Endosc* 2011; **74**: 204-207 [PMID: 21492849 DOI: 10.1016/j.gie.2011.01.071]
101 **Usui N**, Kamata S, Kawahara H, Sawai T, Nakajima K, Soh H, Okada A. Usefulness of endoscopic ultrasonography in the diagnosis of congenital esophageal stenosis. *J Pediatr Surg* 2002; **37**: 1744-1746 [PMID: 12483646 DOI: 10.1053/jpsu.2002.36711]
102 **Sato Y**, Frey EE, Smith WL, Pringle KC, Soper RT, Franken EA.

Balloon dilatation of esophageal stenosis in children. *AJR Am J Roentgenol* 1988; **150**: 639-642 [PMID: 3257622]

103 **Kozarek RA**, Patterson DJ, Ball TJ, Gelfand MG, Jiranek GE, Bredfeldt JE, Brandabur JJ, Wolfsen HW, Raltz SL. Esophageal dilation can be done safely using selective fluoroscopy and single dilating sessions. *J Clin Gastroenterol* 1995; **20**: 184-188 [PMID: 7797822]

104 **Fan Y**, Song HY, Kim JH, Park JH, Ponnuswamy I, Jung HY, Kim YH. Fluoroscopically guided balloon dilation of benign esophageal strictures: incidence of esophageal rupture and its management in 589 patients. *AJR Am J Roentgenol* 2011; **197**: 1481-1486 [PMID: 22109306 DOI: 10.2214/AJR.11.6591]

105 **Chao HC**, Chen SY, Kong MS. Successful treatment of congenital esophageal web by endoscopic electrocauterization and balloon dilatation. *J Pediatr Surg* 2008; **43**: e13-e15 [PMID: 18206438 DOI: 10.1016/j.jpedsurg.2007.08.059]

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REVIEW

Endoscopic treatment for gastrointestinal stromal tumor: Advantages and hurdles

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Abstract

One of the most prominent characteristics of gastrointestinal stromal tumors (GISTs) is their unpredictable and variable behavior. GISTs are not classified as "benign" or "malignant" but are rather stratified by their associated clinical risk of malignancy as determined by tumor size, location, and number of mitoses identified during surgical histology. The difficulty in assessing the malignant potential and prognoses of GISTs as well as the increasing incidence of "incidental GISTs" presents challenges to gastroenterologists. Recently, endoscopic enucleation has been actively performed as both a diagnostic and therapeutic intervention for GISTs. Endoscopic enucleation has several advantages, including keeping the stomach intact after the removal of GISTs, a relatively short hospital stay, a conscious sedation procedure, relatively low cost, and fewer human resources required compared with surgery. However, a low complete resection rate and the risk of perforation could reduce the overall advantages of this procedure. Endoscopic full-thickness resection appears to achieve a very high R0 resection rate. However, this technique absolutely requires a very skilled operator. Moreover, there is a risk of peritoneal seeding due to large active perforation. Laparoscopy endoscopy collaborations have been applied for more stable and pathologically acceptable management. These collaborative procedures have produced excellent outcomes. Many procedures have been developed and attempted because they were technically possible. However, we should first consider the theoretical basis for each technique. Until the efficacy and safety of sole endoscopic access are proved, the laparoscopy endoscopy collaborative procedure appears to be an appropriate method for minimally destructive GIST surgery.

Key words: Gastrointestinal stromal tumor; Endoscopy; Laparoscopy; Efficacy; Safety

Core tip: Several endoscopic approaches have recently been investigated for removing gastrointestinal stromal tumors. Endoscopic enucleation has several advantages. However, there is the possibility of peritoneal seeding when accidental perforation occurs. Furthermore,

the rate of R0 resection is not yet acceptable. While endoscopic full-thickness resection has a more solid theoretical basis than endoscopic enucleation in terms of R0 resection, the possibility of tumor cell shedding into the peritoneum would increase when capsule injury results from the procedure. Compared with endoscopy only procedures, laparoscopy endoscopy cooperative surgery and LAFTR provide a higher complete resection rate and a more stable process, which are accordant with the purpose of minimally destructive surgeries.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) constitute an unusual tumor type that is poorly understood by medical and surgical oncologists. GISTs are the most common mesenchymal tumor of the gastrointestinal tract and are believed to originate from the interstitial cells of Cajal regulating gastrointestinal motility. In the medical literature, GISTs have been confused with true smooth muscle tumors due to their similar features under light microscopy. Once a poorly recognized disease, GISTs have gained increasing interest following advances in diagnostics, both in terms of immunohistochemistry and the characteristic gain of functional mutations in either the *c-KIT* or *PDGFRa* genes, which have been identified as hallmarks of their pathogenesis[1-3]. The presence of c-KIT has been shown through its receptor in approximately 80% of GISTs[4], and 8% of GISTs have mutations in PDGFRa, which encodes a c-KIT-homologous receptor tyrosine kinase[1,2].

The range of clinical feature of GISTs ranges from symptomatic bleeding to incidental detection during a routine endoscopy[5]. In general, 10%-30% of GISTs are clinically malignant[6], but all GISTs are alleged to have some degree of malignant potential[5]. Despite size and location of GISTs are imperative factors facilitating an estimation of the risk of malignancy prior to operation[4,7], dependable preoperative examination for predicting malignancy are not readily available. Endoscopic ultrasonography is useful for obtaining some specimens[8], and the risk of GISTs can be stratified according to several factors[5,7]; for instance, micro-GISTs (no more than 1 cm) generally show benign behavior irrespective of the mitotic rate[9]. However, the difficulty in estimating the malignant potential and the increasing incidence of "incidental GISTs" are particularly challenging for gastroenterologists, who must make decisions regarding patient care and management of this disease; in the case of micro-GISTs, regular endoscopic follow up is generally accepted[10], but R0 resection is frequently considered in cases with larger tumors.

Endoscopic enucleation and related variations of this treatment have recently been introduced for managing GISTs, most often in incidentally detected cases. There are several advantages of endoscopic treatment, but it presents some risks as well. Endoscopic full-thickness resection (EFTR), laparoscopy endoscopy cooperative surgery (LECS), laparoscopy-assisted endoscopic full-thickness resection (LAEFR), and non-exposed wall-inversion surgery (NEWS) have been applied for more pathologically acceptable management. This article provides an overview of the theoretical basis and technical feasibility of gastric GIST treatment in terms of an endoscopic approach with or without laparoscopic collaboration, considering the imperative points of conventional surgical resection.

THEORETICAL BASIS

Incidental GIST

Endoscopic enucleation is typically performed for asymptomatic GISTs. Approximately 15%-30% of GISTs were incidentally discovered without presenting any symptoms[6,11,12]. In these studies, the incidental discovery of GISTs primarily occurred after surgical resection for other reasons or during postmortem examination. Several studies have noted the existence of subclinical microscopic gastric GISTs[13-16]. Microscopic gastric GISTs were discovered in 22.5% of consecutive autopsies conducted on patients aged no less than 50 years old[15]. Kawanowa *et al*[16] presented evidence that microscopic GISTs were observed in 35% of whole stomachs that were surgically resected due to gastric carcinoma. As upper gastrointestinal examination by endoscopy has been increased, the incidental recognition of subepithelial lesions has also substantially increased. According to one retrospective study, the prevalence of subepithelial gastric lesions was 0.36% during routine exanimation[17]. These studies show that GISTs are far more common than previously presumed. Considering this suggestion, a gastroenterologist may frequently encounter GISTs in normal clinical practice, and a practical guide should be established to avoid irregular management of incidentally detected GISTs.

Malignant potential

Importantly, all GISTs are thought to have some degree of malignant potential. Approximately 20%-25% of GISTs in the stomach demonstrate malignant behavior[4]. One of the most prominent features of GISTs is unpredictable and variable behavior. Large, presumably aggressive GISTs can progress in an indolent manner, whereas small, incidentally discovered GISTs can show malignant behavior. Thus, GISTs are not classified as "malignant" or "benign" but are rather stratified by the clinical

Table 1 Prognostication of gastrointestinal stromal tumor atdifferent sites by tumor size and mitotic rate based on follow-up studies of over 1700 gastrointestinal stromal tumors prior to imatinib

Tumor parameters			Percentage of patients with progressive disease during long-term follow-up and quantitative characterization of the risk for metastasis			
Group	Size	Mitotic rate	Gastric GISTs	Small intestinal GISTs	Duodenal GISTs	Rectal GISTs
1	≤ 2 cm				0 none	
2	> 2 ≤ 5 cm	≤ 5/50	1.9 (very low)	4.3 (low)	8.3 (low)	8.5 (low)
3a	> 5 ≤ 10 cm	HPFs	3.6 (low)	24 (moderate)	34 (high)[1]	57 (high)[1]
3b	> 10 cm		12 (moderate)	52 (high)		
4	≤ 2 cm		0[1]	50[1]	[2]	54 (high)
5	> 2 ≤ 5 cm	> 5/50	16 (moderate)	73 (high)	50 (high)	52 (high)
6a	> 5 ≤ 10 cm	HPFs	55 (high)	85 (high)	86 (high)[1]	71 (high)[1]
6b	> 10 cm		86 (high)	90 (high)		

[1]Small number of cases. Groups combined or prognostic prediction less certain; [2]No tumors encountered with these parameters. (Adopted from Miettinen *et al*[4]). HPF: High power field; 50 high: Power fields equal approximately 5 mm^2; GIST: Gastrointestinal stromal tumor.

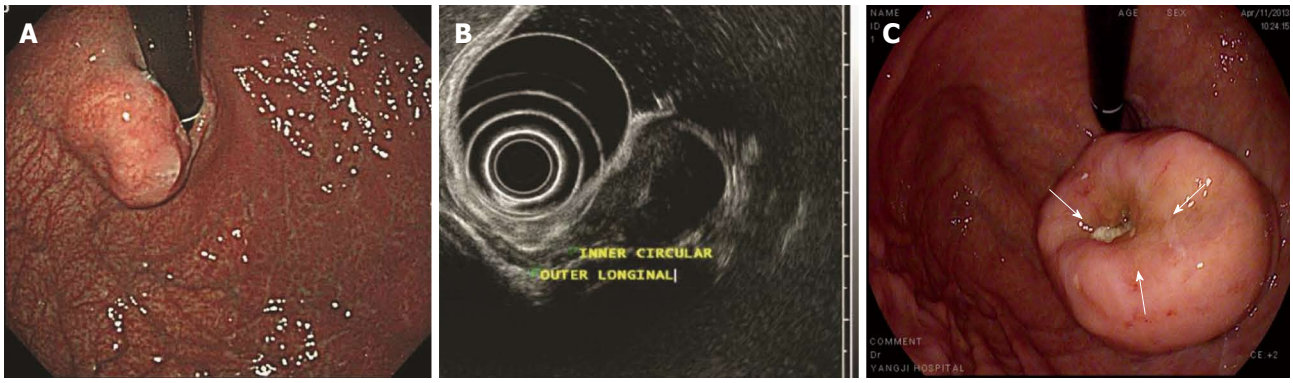

Figure 1 Features of gastrointestinal stromal tumors. A: An approximately 2-cm elevated lesion covered with nearly intact mucosa was observed at the cardia; B: EUS demonstrated a 21-mm, generally homogenous hypoechoic, well circumscribed pear-shaped lesion originating from the inner circular layer of the proper muscle layer. Inside the lesion, a hyperechoic septum-like structure was noticed; C: There was a small deep focal ulceration at the center of the gastrointestinal stromal tumor (GIST) (white arrows).

risk of malignancy depending on mitotic count, size, location (Table 1)[7]. A preoperative estimation of risk can be induced from size and location, but reliable criteria for surgery do not currently exist. Unlike gastric adenocarcinomas, regional lymph node metastasis of GIST is unusual; the prevalence has been reported to range from 1.1% to 3.4%[18-20]. Because it is difficult to predict the malignant behavior of GISTs, together with the rarity of lymph node metastasis, the theoretical basis for endoscopic removal can be reasonably supported if this method results in complete resection and does not cause peritoneal seeding.

Gross appearance and location in the gut wall

To estimate the feasibility of endoscopic procedures, it is important to understand the gross findings. GISTs range in size from a few mm to 35 cm, with a median size between 5 and 8 cm[11,21]. The targets of endoscopic enucleation and related procedures are small- to medium-sized gastric GISTs less than 5 cm in size. Small- to medium-sized GISTs typically form a well-delineated spherical or hemispherical mass, arising mostly from the proper muscle (PM) layer beneath the mucosa and pushing into the lumen to form a smooth-contoured elevation (Figure 1A and B).Focal mucosal ulceration is common in GISTs at all sites (Figure 1C) and is not related to tumor malignancy. GISTs are usually well circumscribed and surrounded by a pseudocapsule. The presence of a pseudocapsule contributes to the indication for complete resection in endoscopic enucleation.

When considering endoscopic enucleation, GISTs must be classified into several types according to their locations in the gastric wall (Figure 2). Type Ⅰ is a GIST that has a very narrow connection with the PM and protrudes into the luminal side, similar to polyps (Figure 2A). Type Ⅱ has a wider connection with the PM and protrudes into the luminal side at an obtuse angle (Figure 2B). Type Ⅲ is located in the middle of the gastric wall (Figure 2C). Type Ⅳ protrudes mainly into the serosal side of the gastric wall (Figure 2D). Of the four types, type Ⅰ is the best candidate for endoscopic enucleation due to its narrow connection with the PM layer, and it seems possible to remove type Ⅱ lesions by endoscopic enucleation. However, it is nearly impossible to achieve complete resection of type Ⅲ and type Ⅳ GISTs by endoscopic enucleation. Thus, EFTR, LECS, LAEFR, or NEWS should be considered for

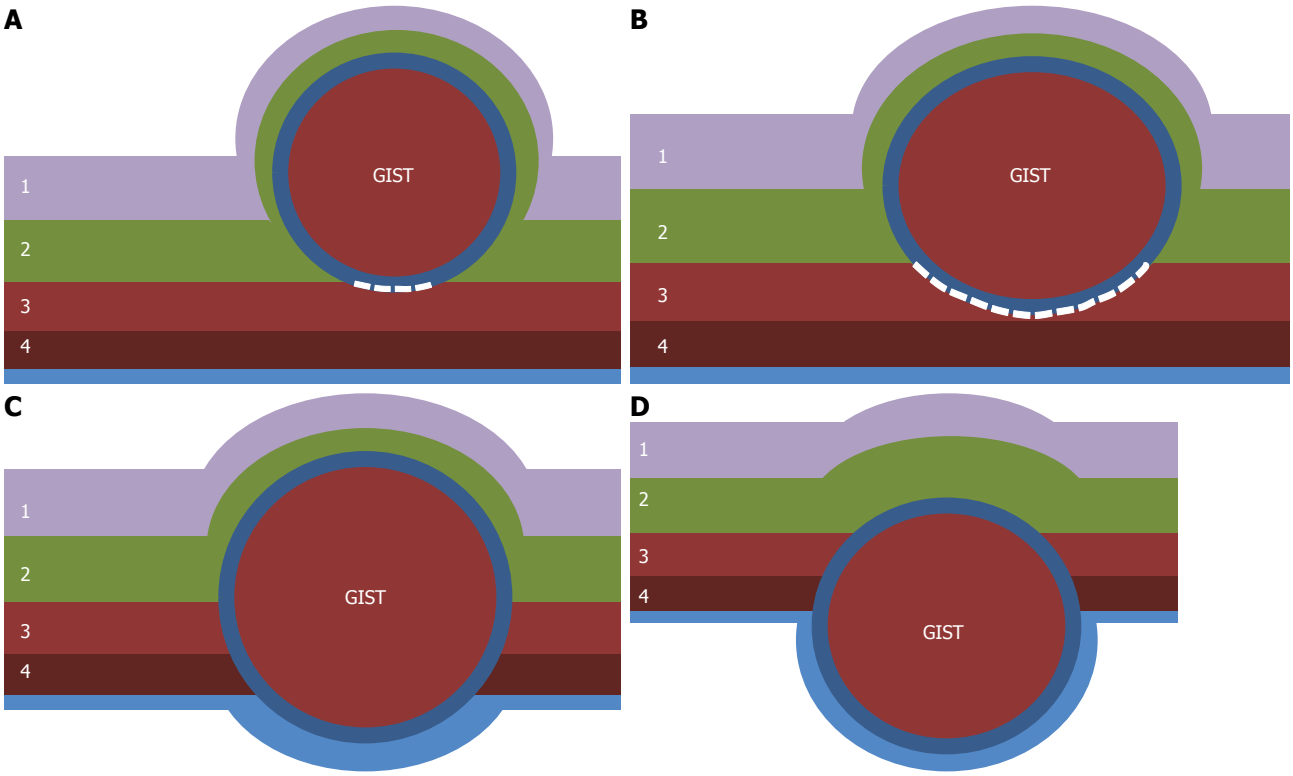

Figure 2 Classification of gastrointestinal stromal tumors according to the location in the gastric wall. A: Type Ⅰ is a gastrointestinal stromal tumor (GIST) that has a very narrow connection with the proper muscle layer and protrudes into the luminal side like a polyp; B: Type Ⅱ has a wider connection with the proper muscle layer and protrudes into the luminal side at an obtuse angle; C: Type Ⅲ is located in the middle of the gastric wall; D: Type Ⅳ protrudes mainly into the serosal side of the gastric wall. White dotted lines indicate the area dissected from the proper muscle layer. 1: Mucosa; 2: Submucosa; 3: Circular layer of proper muscle; 4: Longitudinal layer of proper muscle.

type Ⅲ and Ⅳ GISTs.

Surgical resection and follow-up program

Surgical removal is the primary treatment for a localized GIST in the majority of cases. Prior to evaluating the feasibility of therapeutic endoscopic procedures for GISTs, it is necessary to understand the surgical procedures and outcomes as a conventional standard strategy. The primary goal of surgery is complete tumor removal with clear resection margins. Avoiding pseudocapsule rupture is very important because intra-abdominal dissemination and a poor prognosis have been seriously associated with its occurrence[22]. It seems not necessary to perform routine lymphadenectomy due to rare nodal metastasis[23].

Depending on the location of the lesion, the type of surgery is determined. In cases of esophageal, small intestinal, and rectal GISTs, wide resections are the surgery of choice[24]. Gastric wedge resection is the most frequently performed procedure for gastric GISTs, and it is recommended as the treatment of choice; however, in some cases, tumor size and location may indicate extensive surgery, including a partial or total gastrectomy. Laparoscopic wedge resection, which is less invasive than the traditional technique, has been demonstrated to have comparable results in terms of efficacy, safety profile, and length of hospitalization[25-32]. Short- and long-term outcomes of laparoscopic wedge resection have been shown to be equivalent to the open surgical approach. Guidelines suggest that laparoscopic wedge resection can be used for tumors ≤ 5 cm[22]. Laparoscopic approaches to GIST management continue to expand and should adhere to standard oncological principles, including avoidance of direct grasping and tumor rupture, and an extraction bag is recommended when tumors are removed[31,33-37]. Although a microscopically positive margin was not found to be a significant adverse factor in some studies[23,38], one study did find it to be an adverse factor for survival[39].

The guidelines of the national comprehensive cancer network recommended abdominal and pelvic CT scan every 3-6 mo for 3-5 years and annually thereafter following completer resection[22]. Less frequent surveillance may be acceptable for small tumors (< 2 cm). Currently, Imatinib is approved both in the United States and the EU as an adjuvant therapy for GIST after surgical resection.

TECHNICAL FEASIBILITY OF THE ENDOSCOPIC APPROACH

Nearly all interventions have been performed for submucosal tumors originating from the PM layer without validating preoperative histological findings. Therefore, it is realistic to estimate the feasibility of an endoscopic approach for GIST by accessing data

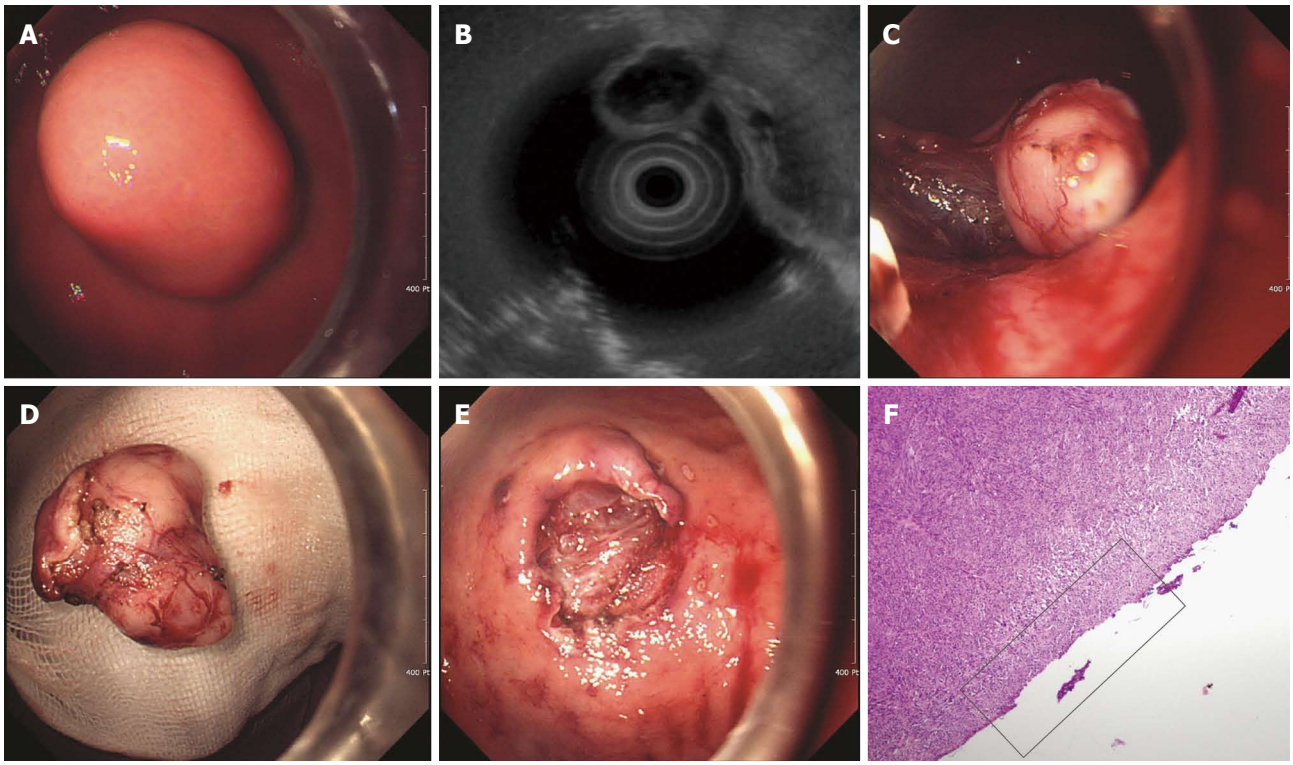

Figure 3 Endoscopic enucleation using the standard endoscopic submucosal dissection technique. A: An approximately 2.5-cm subepithelial tumor was identified at the greater curvature side of the upper body of the stomach; B: A 2.6-cm mixed echogenic tumor with a slightly irregular border arising from the proper muscle layer was noticed; C: Endoscopic enucleation using the endoscopic submucosal dissection technique was performed; D: *En bloc* resection was achieved; E: There was no perforation at the operation site; F: On pathologic examination, a vertical resection margin was apparently involved with tumor cells (red boxed area); R1 resection was confirmed. (Courtesy of Kyung Oh Kim, Gil hospital, Incheon, South Korea).

acquired from submucosal lesions originating from the PM layer.

ENDOSCOPIC ENUCLEATION

Submucosal endoscopic dissection

GISTs originating from the PM layer are not likely to be removed completely and safely using standard or modified endoscopic submucosal dissection (ESD). In such cases, deep submucosal dissection and PM layer resection should be performed. Moreover, the PM layer under the lesion must be carefully dissected (Figure 3). Thus, perforation risk is inevitably high. Furthermore, the margin seems to be minimal and easily involved in tumor cells (Figure 3F); there is also a potential risk of injury to the pseudocapsule. Several studies presented similar rates of successful *en bloc* resection (64%-94%) and perforation rates from 0% to 12% using ESD for GISTs originating from the PM layer (Table 2) (n = 11, 25, and 22)[40-42]. The imperative point, which should be noted, is that not all studies assessed pathologic evaluation, although they insisted on complete resection (n = 11 and 25)[40,41]. One recent study (n = 86) reported a 5.8% local recurrence rate after endoscopic enucleation of 86 GISTs, although all of the GISTs were completely removed endoscopically[43].

Endoscopic muscularis dissection

Liu *et al*[44] introduced another endoscopic technique, called endoscopic muscularis dissection (EMD), for tumors originating from the PM layer (n = 31, 14 esophageal and 17 gastric tumors)[44]. Of these tumors, 97% (30/31) were completely resected. The perforation rate was 13% (4/31)[44]. A longitudinal incision may have advantages in closing the mucosa with clips and promoting wound healing (Figure 4).

Endoscopic submucosal tunnel dissection

Endoscopic submucosal tunnel dissection (ESTD) is an innovative method that provides a solution for perforation, which frequently occurs during proper muscle dissection. The first case was reported by Inoue *et al*[45], submucosal endoscopic tumor resection for cardial and esophageal subepithelial tumors (n = 7)[45]. Submucosal tunnel dissection includes four major procedures (Figure 5): (1) creating a submucosal tunnel; (2) dissecting the tumor from the mucosa or submucosa; (3) dissecting the PM layer attached to the tumor; and (4) retrieving the specimen and closing the mucosal entry site with clips (n = 7, 12, and 85)[45-47]. The imperative advantage of ESTD is maintaining mucosal integrity during *en bloc* resection of subepithelial tumors (n = 143)[48]. ESTD may possibly decrease the risk of gastrointestinal tract leakage and subsequent infection[48]. Therefore, this technique may be a promising novel method for selected[46] GISTs arising from the PM layer at the cardia, particularly because endoscopic enucleation in this area can result

Table 2 Recent publications reporting endoscopic enucleation and endoscopic full-thickness resection for upper gastrointestinal tumors originating from the proper muscle layer

Ref.	*n*	Method	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complications/recurrence
Wang *et al*[43] (2014)	86	Standard ESD	-	-	100	4 delayed bleedings 9 perforations 5 local recurrences
Ye *et al*[47] (2014)	85	ESTD	57	19	100	4 pneumothorax and subcutaneous emphysema 2 pneumothorax 2 subcutaneous emphysema
Feng *et al*[49] (2014)	48	EFTR	60	16	100	0
Li *et al*[48] (2012)	143	ESD (134), EFTR (6), ESTD (3)	45	18	94[1]	2 pneumothorax, 1 subcutaneous emphysema
Białek *et al*[42] (2012)	22	Standard ESD	-	-	68[1]	2 perforations
Liu *et al*[44] (2013)	31	EMD	77	22	97	4 perforations
Inoue *et al*[45] (2012)	7	SET	152	19	100	0
Gong *et al*[46] (2012)	12	ESTD	48	20	83	2 pneumothorax and subcutaneous emphysema
Zhou *et al*[52] (2011)	26	EFTR	105	28	100	0
Hwang *et al*[41] (2009)	25	ESD	-	29	64	3 perforations
Lee *et al*[40] (2006)	11	ESD	61	21	75	0

[1]Pathologically evaluated. EFTR: Endoscopic full-thickness resection; EMD: Endoscopic muscularis dissection; ESD: Endoscopic submucosal dissection; ESTD: Endoscopic submucosal tunnel dissection; SET: Submucosal endoscopic tumor resection.

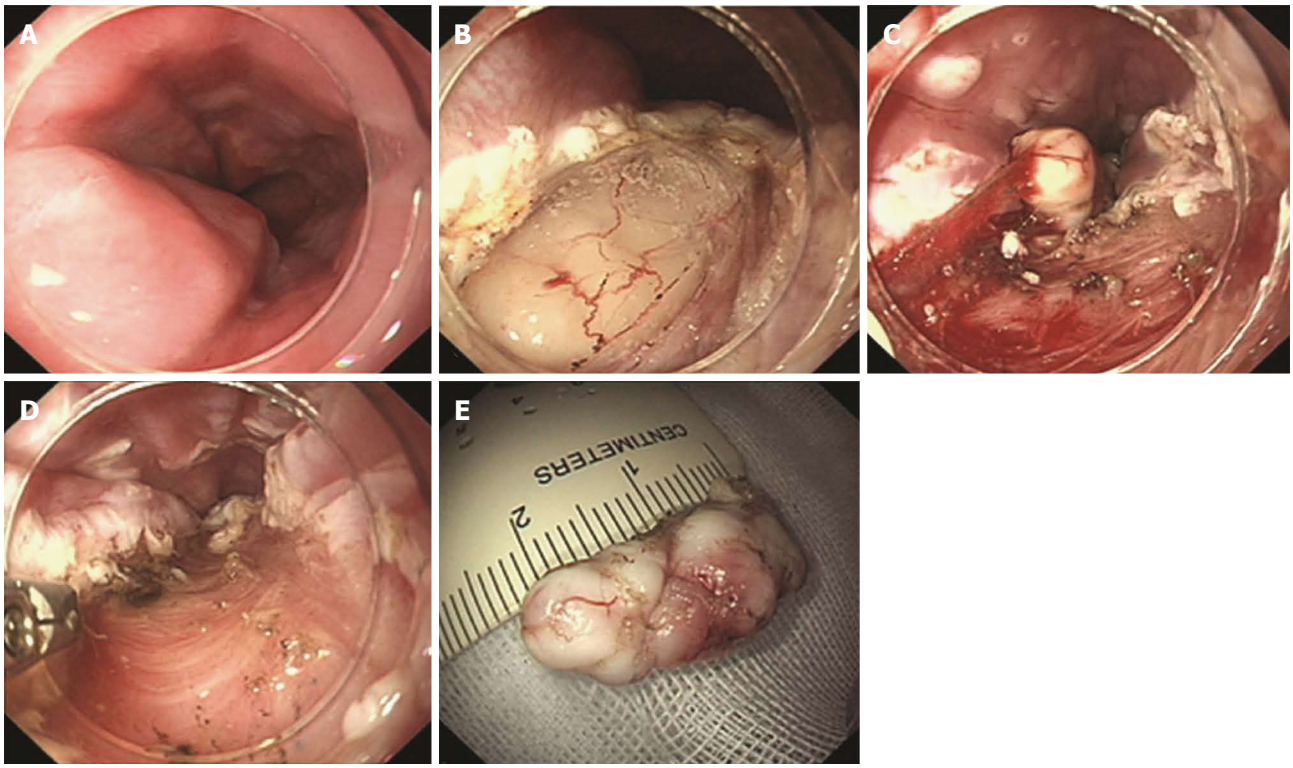

Figure 4 Endoscopic muscularis dissection of an esophageal subepithelial tumor originating from the proper muscle layers. A: Endoscopic view of the esophageal submucosal tumor; B: Exposure of the tumor using a longitudinal incision; C: Blunt dissection of the tumor as deep as the proper muscle layer with a transparent hood; D: Stopping bleeding after blunt dissection; E: The whole tumor was removed F: Linear clipping was performed to close the submucosal entry site (adopted from Liu *et al*[44]).

in pneumothorax and subcutaneous emphysema[46,47].

Advantages and drawbacks

Given the safety and efficacy of endoscopic enucleation, these emerging techniques can be preferable options for GISTs arising from the PM layer who are admitted to institutions with experienced operators. Endoscopic enucleation has several advantages, such as an intact stomach after GIST removal, a relatively short hospital stay, a conscious sedation procedure, relatively low

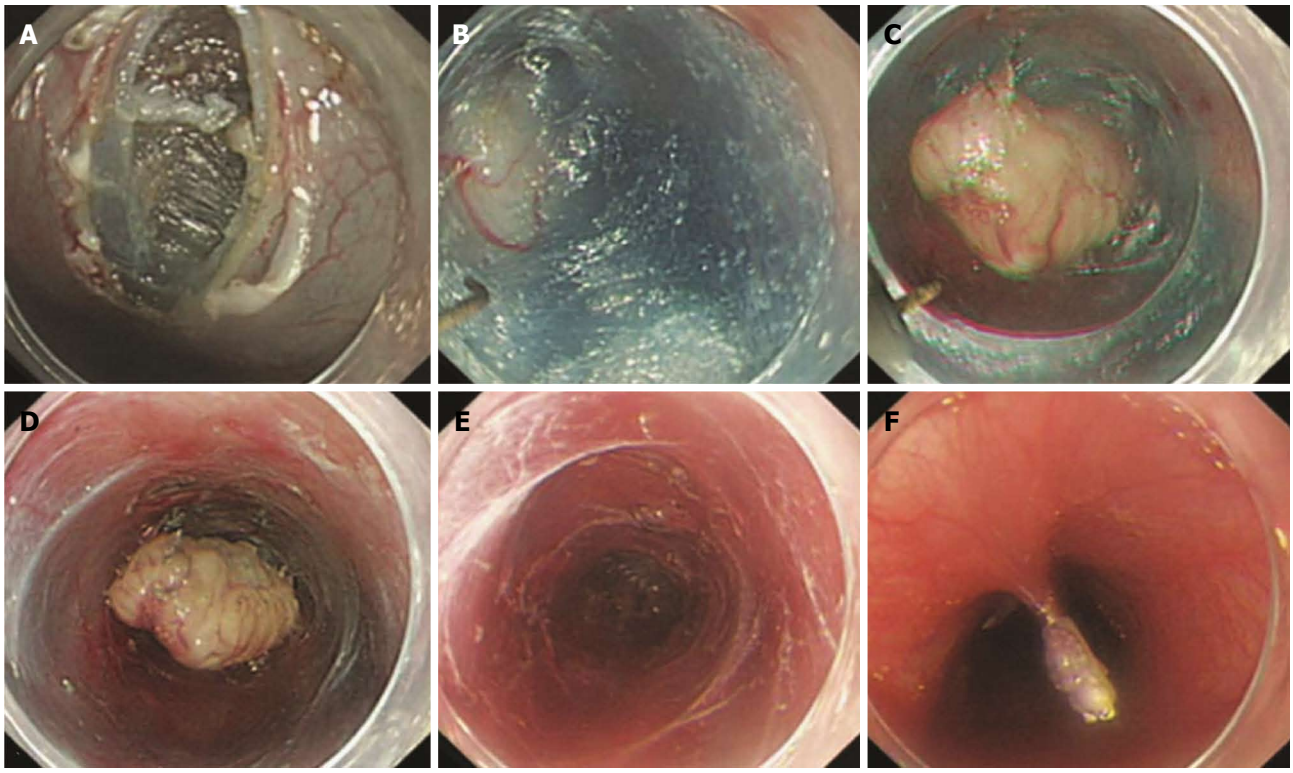

Figure 5 Endoscopic submucosal tunnel dissection procedure with longitudinal access. A: A 2-cm longitudinal mucosal incision was created, approximately 5 cm over the submucosal tumor; B: Submucosal dissection was performed, making a submucosal tunnel until the tumor was visible; C: Dissection was performed along the margin of the tumor; D: Dissection was completed; E: After removing the tumor, potential bleeding foci were coagulated; F: Closing the entry with clips (adopted from Gong *et al*[46]).

cost, and fewer human resources required compared with surgery.

However, it should be noted that several disadvantages also exist, which must be overcome to ensure the efficacy and safety of these advanced endoscopic techniques. First, there have been no data showing whether or not there was remnant GIST tissue at dissection sites when R1 resection was conducted; most studies have only validated *en bloc* resection[40,41,44,46,47,49]. The dissection surface was ablated by an electrical knife or snare, so there may not be remnant GIST cells, although R1 resection was achieved. Although this assertion seems logical, there have been no data proving this hypothesis. Moreover, one of the latest studies reported that a 5.8% local recurrence was observed even though complete endoscopic resection was achieved in all cases. To address this hypothesis, surgical resection of the dissected area should be obtained, and a careful pathological examination of the dissected surface must be conducted. Although several studies have shown that a microscopically positive margin was not a significant adverse factor[23,38], we should understand that these were surgical outcomes. In laparoscopic surgery, staples are used for the procedure, and the additional tissue from the resection line is essentially removed, indicating that R1 resection of GIST specimens during surgical procedures includes cases with R0 resection in a remnant stomach. In contrast, endoscopic enucleation does not involve this additionally removed area. There has also been disagreement regarding this result even in conventional surgical procedures[39]. Considering this information, R1 resection in endoscopic enucleation should be regarded as true R1 resection until appropriate studies demonstrate contrasting evidence. Currently, post-procedural management of R1 resection should be additional surgery, particularly for R1 resection of intermediate- to high-risk GISTs.

Second, because perforation is usually accompanied by pseudocapsule injury, the possibility of peritoneal seeding increases. Peritoneal seeding is accompanied by a high recurrence rate and can result in a poor prognosis. If PM layer dissection does not cause perforation, capsule injury may not be a serious problem; the tumor cells will shed into the lumen of the gut and will be destroyed. However, there is some likelihood of concomitant perforation and capsule rupture or injury during the procedure, particularly in cases where there is difficulty in conducting the procedure. In such situations, shedding of tumor cells into the peritoneal cavity is predicted. Currently, no comparative data with conventional surgical outcomes exist.

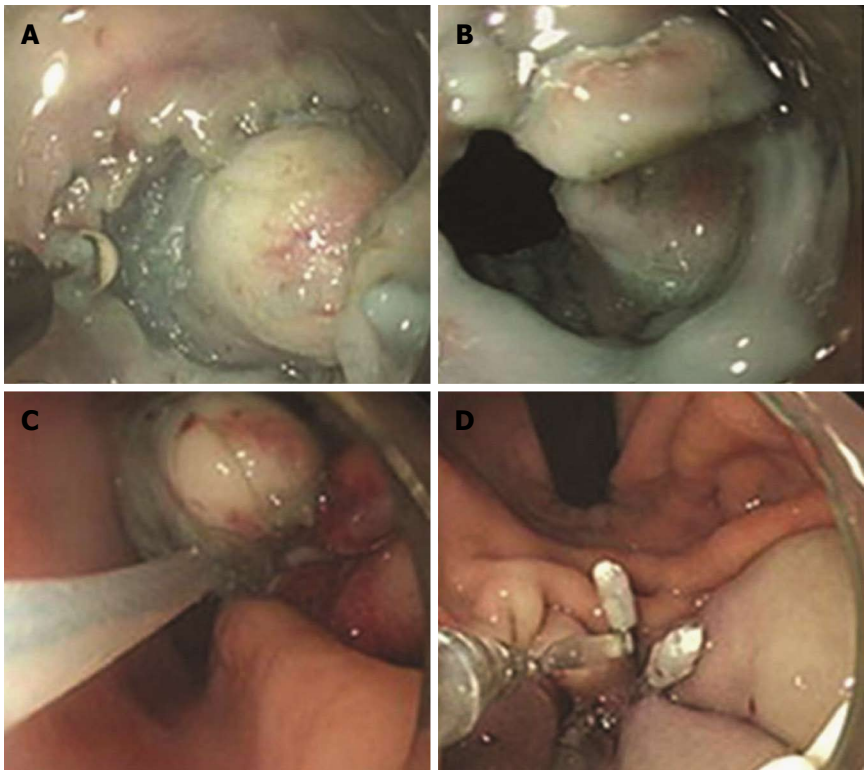

Figure 6 Procedure for endoscopic full-thickness resection of gastric subepithelial tumors originating from the proper muscle layer. A: A circumferential incision was made as deep as the proper muscle layer around the lesion with an IT knife; B: The tumor protruded into the peritoneal cavity after active perforation due to the incision into the serosal layer around the lesion; C: The tumor and surrounding tissue were pulled into the gastric cavity; D: The gastric wound was successfully closed with several metallic clips (adopted from Zhou *et al*[52]).

ENDOSCOPIC FULL-THICKNESS RESECTION WITHOUT LAPAROSCOPIC ASSISTANCE

The first case of EFTR using a snaring technique was reported in 2001[50]. Ikeda *et al*[51] recently presented EFTR by ESD in a swine stomach. This trial demonstrates an important step forward in endoscopic surgery, but it is currently not likely applicable in clinical settings. The risk of peritoneal infection and skeptical views of complete closure cause potentially major concerns in endoscopy-only procedures. Thus, EFTR should overcome the prevalent idea that perforation is a serious complication. However, Zhou *et al*[52] (n = 26) and Feng *et al*[49] (n = 48) succeeded in the use of EFTR for resecting gastric SMTs originating from the PM layer without laparoscopic assistance (Table 2). Their EFTR technique was based on standard ESD and consisted of four major procedures (Figure 6): (1) a circumferential incision as deep as the PM layer; (2) Creating active perforation by serosal layer incision; (3) removing a tumor and its surrounding PM and serosal layers by snare; and (4) closing active perforation site by several clips[49,52]. *En bloc* resection was achieved in all cases[49,52]. Furthermore, there were no serious complications[49,52]. According to these two studies, EFTR appears to be an ideal minimally destructive measure for gastric GISTs. One thing that should be noted is that EFTR essentially creates a large active perforation, which can result in the shedding of tumor cells into the peritoneum when the pseudocapsule is not intact. Thus, gentle maneuvering is required to maintain an intact pseudocapsule. The efficacy and safety of EFTR must be validated in multicenter studies to standardize this promising technique.

LAPAROSCOPIC ENDOSCOPIC COLLABORATIVE PROCEDURES

For the first time, a combination of gastrointestinal endoscopy and laparoscopy has been reported for removing esophageal subepithelial tumor by Izumi *et al*[53]. In this technique, a subepithelial tumor was pushed out by a balloon on an endoscope, and thoracoscopic enucleation was performed to remove the protruded tumor[53,54]. Hiki *et al*[55] (n = 7) reported the successful use of ESD for assisting local laparoscopic gastric resection to remove a GIST. In their technique, named LECS, laparoscopic multiple staplers were used for resection after approximately three-fourths cutline was completed by ESD. Tsujimoto *et al*[56] presented satisfactory surgical outcomes after LECS for gastric subepithelial tumor also (n = 20). Reducing the resected gastric wall volume is an important advantage of LECS compared with conventional laparoscopic wedge resection solely using

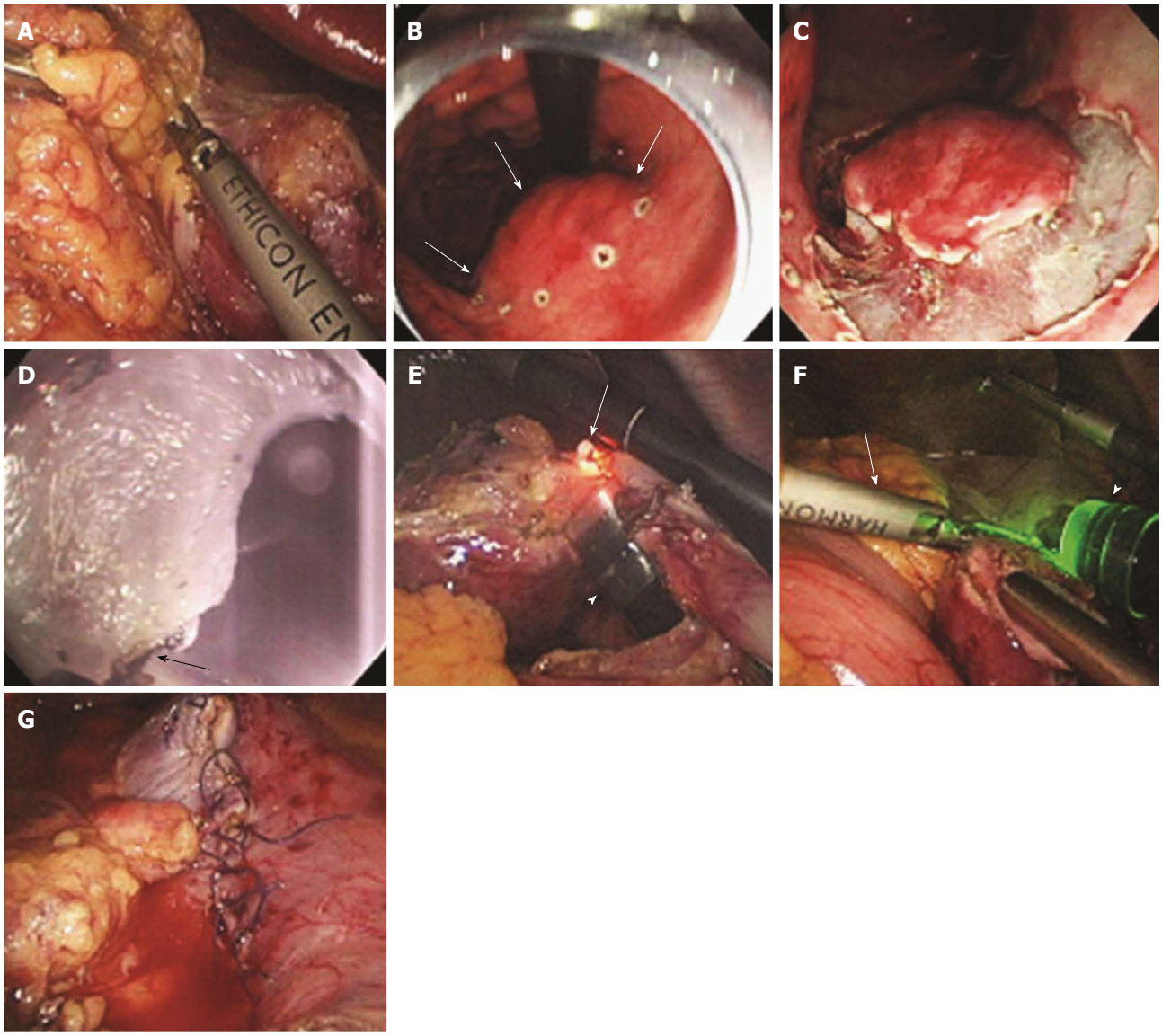

Figure 7 Procedure for laparoscopy-assisted endoscopic full-thickness resection. A: Laparoscopic view while the lesser omentum attached around the tumor site was dissected; B: Endoscopic view after marking around the gastric subepithelial tumor (white arrows) located on the lesser curvature side of the gastric body; C: Gastroscopic view after incision as deep as the submucosal layer around the lesion; D: Gastroscopic view of the full-thickness incision from inside the stomach using the IT knife (white arrow); E: Laparoscopic view of the full-thickness incision from inside the stomach using the IT knife (arrow, the tip of the IT knife; arrowhead, the gastroscope); F: Laparoscopic view of the remaining full-thickness incision from outside the stomach using a Harmonic ACE (arrow); G: Laparoscopic view after laparoscopic hand-sewn closure of the gastric-wall defect (adopted from Abe *et al*[58]).

a linear stapler[57].

LAEFR, *i.e.*, EFTR with laparoscopic assistance, is an effective treatment for selected patients with gastric subepithelial tumors (n = 4 and 25)[58,59]. There are four major steps in LAEFR (Figure 7): (1) deep submucosal incision using ESD[57]; (2) endoscopic seromuscular layer incision, three-fourths or two-thirds of the circumference; (3) laparoscopic seromuscular incision for remaining circumference; and (4) hand-sewn closure. The different point of LAEFR from LES is a hand-sewn closure without linear staples. LECS affords easier and more accurate resection, and the LAFTR results in minimal resection[57]. LECS and LAFER showed excellent outcomes. All reports have shown 100% complete resection rates and no complications (Table 3)[55,56,58,59]. The best indication for LECS and LAEFR may be intraluminal growing types of gastric GISTs originating from the PM layer. Such lesions cannot be well identified from the serosal side of the stomach; therefore, there is a high probability that conventional laparoscopic wedge resection will cause a larger-than-expected resection and bring about a gastric deformity or stenosis, or conversely, can produce a positive surgical margin[57]. LECS or LAEFR can avoid such problems. Full-thickness resection procedures are derived from ESD. Therefore, both can be applied regardless of tumor size, and a pathologically acceptable resection margin can be more easily accomplished[57-60].

NEWS is a newly suggested technique developed

Table 3 Publications reporting laparoscopic and endoscopic cooperative surgery, laparoscopy-assisted endoscopic full-thickness resection, and non-exposed wall-inversion surgery for submucosal tumors in the upper gastrointestinal tract

Ref.	*n*	Method	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complications
Mitsui *et al*[61] (2014)	6	NEWS	306	34	100	0
Hoteya *et al*[59] (2013)	25	LAFER	156	32	100[1]	0
Tsujimoto *et al*[56] (2012)	20	LECS	157	38	100[1]	0
Hiki *et al*[66] (2011)	38	LECS			100	0
Abe *et al*[58] (2009)	4	LAEFR	201	30	100[1]	0
Hiki *et al*[55] (2008)	7	LECS	169	46	100	0

[1]Pathologically evaluated. LAEFR: Laparoscopy-assisted endoscopic full-thickness resection; LECS: Laparoscopic and endoscopic cooperative surgery; NEWS: Non-exposed wall-inversion surgery.

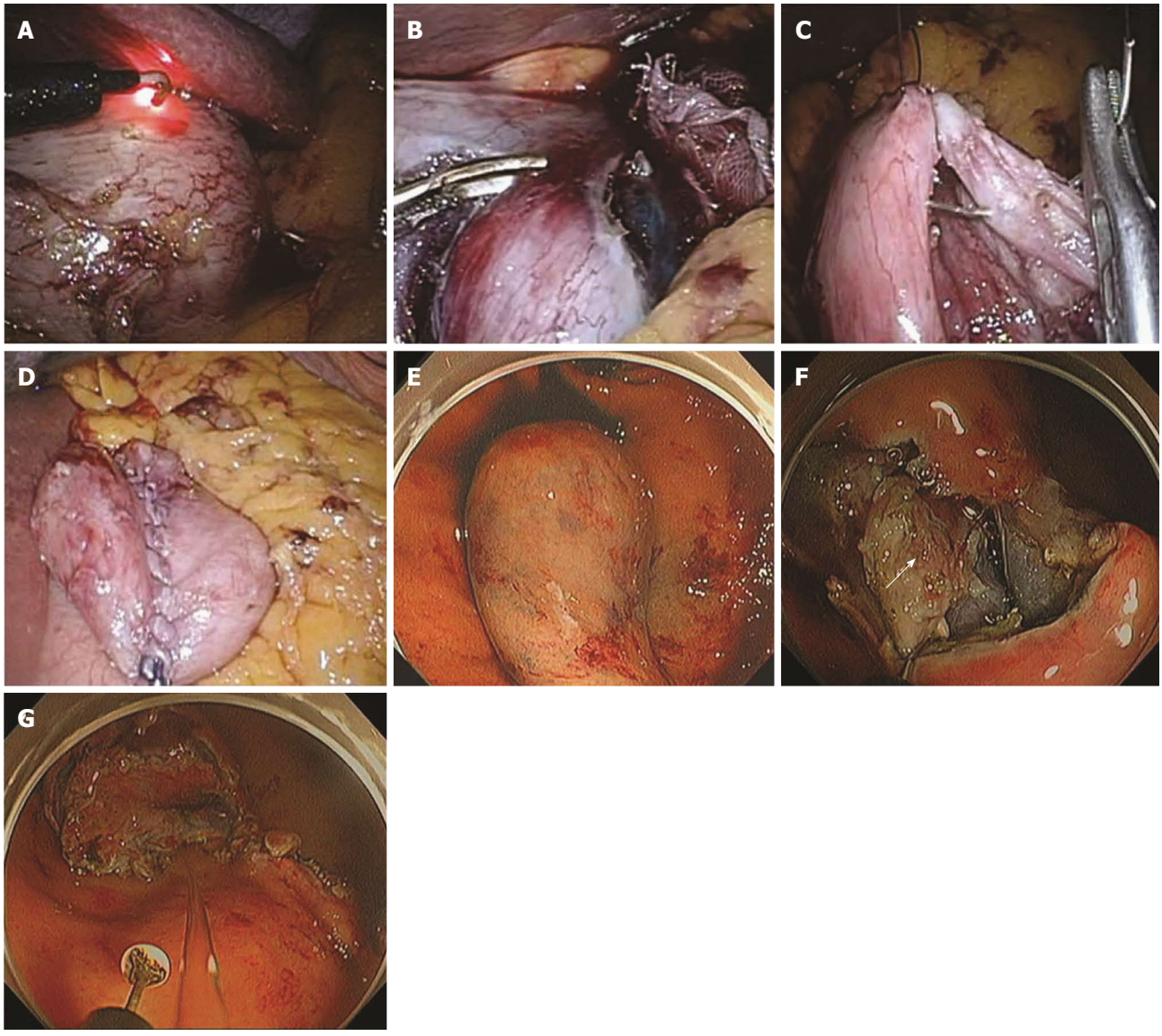

Figure 8 Procedure for non-exposed wall-inversion surgery. A: Laparoscopic markings on the serosal surface guided by light from the fiber-optic probe shining through the gastric endoscope; B: Circumferential seromuscular layer dissection outside the serosal markings; C: Seromuscular layer suture closure; D: Laparoscopic view of inversion of the dissected area; E: Endoscopic view of massive protrusion of the inverted tissue; F: Serosal surface (arrow) identified during mucosubmucosal layer dissection; G: Flipped tissue to be resected (adopted from Mitsui *et al*[61]).

to minimize the resected tissue volume as well as prevent peritoneal contamination (n = 6)[61]. There are 7 major steps in NEWS (Figure 8)[61,62]: (1) marking the mucosa around a lesion; (2) serosal marking using laparoscopy on the side opposite the mucosal markings; (3) injecting hyaluronate solution endoscopically into the submucosal layer; (4) laparoscopic circumferential seromuscular

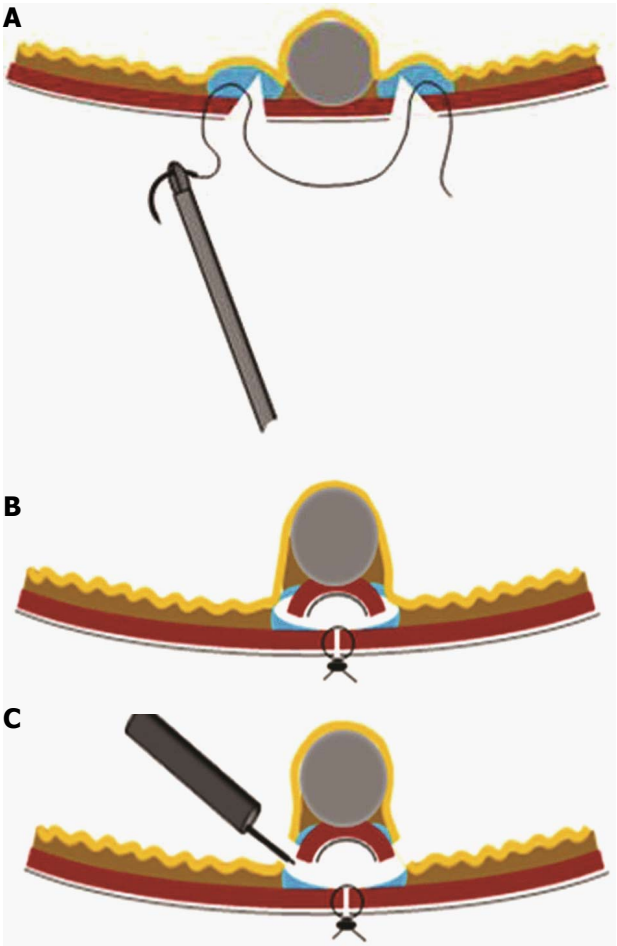

Figure 9 Scheme of the procedure for non-exposed wall-inversion surgery. A: Seromuscular layer suture after submucosal injection and seromuscular cutting; B: Divided seromuscular layer inversion after laparoscopic seromuscular closure; C: Mucosubmucosal layer dissection (adopted from Mitsui *et al*[61]).

layer incision; (5 suturing the seromuscular layer; (6) spontaneous inversion of the lesion; and (7) circumferential incision of the mucosubmucosal layer. Theoretically, this technique nearly perfectly prevents peritoneal contamination because seromuscular layer suture and closure is performed before mucosubmucosal layer cutting (Figure 9)[61]. However, this innovative technique contains a few downsides compared with LECS or LAEFR. Mitsui *et al*[61] reported 2 perforations in 6 cases: one laparoscopic mucosal injury during the seromuscular incision and musculoserosal tearing by ESD. Two cases out of 6 also converted due to poor recognition of the tumor margin[61]. Selecting appropriate lesions, type Ⅲ and type Ⅳ, and advancement of this technique would be necessary to apply NEWS in ordinary clinical fields.

IMATINIB AS AN ADJUVANT TREATMENT

Although a significant proportion of patients will be cured with surgery alone, approximately 40% will eventually have a relapse of disease, with the majority of these relapses occurring within the first 5 years. The ACOSOG Z9001 trial[63] compared 12 mo of imatinib treatment with a placebo and showed an estimated 1-year recurrence-free survival (RFS) of 98% in the Imatinib group compared with 83% in the placebo group (HR: 0.35). More recently, the Phase Ⅲ Scandinavian Sarcoma Group Trial[64] reported that patients affected by GISTs with a high risk of recurrence treated with adjuvant Imatinib for 36 mo had longer RFS (5-year RFS, 65.6% *vs* 47.9%; HR: 0.46) and improved overall survival (5-year survival, 92% *vs* 81.7%; HR: 0.45) compared with those receiving 12 mo of treatment. These trials provided Level 2 evidence, according to the latest edition of the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence, for the role of adjuvant imatinib in patients with resected GISTs. Together, the current evidence supports at least 3 years of adjuvant imatinib as a new standard for patients with resected, high-risk GISTs, although the optimal duration of therapy remains unknown[65]. In endoscopic enucleation, imatinib treatment appears to often be neglected, possibly for the following reasons. First, a lesion removed by endoscopic enucleation is typically small- to medium-sized. Second, most GISTs were incidentally detected in asymptomatic patients unlike gastric cancer cases, which are typically more serious and draw greater attention from doctors and surgeons. However, it is absolutely desirable for practitioners to follow the guidelines for adjuvant usage of imatinib, based on the risk level of the GISTs.

CONCLUSION

Unpredictable malignant potential and rare lymph node metastasis provided the theoretical basis for the concept of minimally destructive surgery for incidentally detected asymptomatic GISTs. Under this theoretical concept, technical advances have been made based on ESD-enabled surgeons performing endoscopic enucleation of GISTs. However, there is the possibility of simultaneous occurrence of perforation and pseudocapsule injury, which can cause peritoneal seeding. Furthermore, the rate of R0 resection is not yet acceptable, although one study reported a high R0 resection rate. Well-trained surgeons and a more secure endoscopic enucleation technique are needed to justify the implementation of this procedure. Moreover, long-term results of endoscopic enucleation will be necessary to confirm the true efficacy and safety because reports on the use of endoscopic enucleation are currently limited to case reports and small, retrospective, or pilot series. While EFTR has a much better theoretical basis than endoscopic enucleation in terms of R0 resection, the possibility of tumor cell shedding into the peritoneum would substantially increase when capsule injury results from the procedure. Moreover, a surgeon needs advanced

skills to close a large iatrogenic perforation. In contrast with procedures that employ only endoscopy, LECS and LAFTR provide safer procedures, a higher complete resection rate, and a more stable process. Although LECS and LAFTR require more resources, including more people, more devices, and even additional machines, LECS and LAFTR could represent more acceptable procedures in terms of conventional surgical purposes, because they result in complete resection and avoid peritoneal seeding.

Various endoscopic procedures have challenged conventional surgery with the aid of advances in modern medical technology. Many procedures were invented and attempted because they were technically possible. However, we should consider the aim of conventional surgery, which has accumulated vast data. Until the efficacy and safety of sole endoscopic access are demonstrated in multiple ways, LECS and LAFTR appear to be appropriate procedures for pursuing secure and effective surgical outcomes that conform to the concept of minimally destructive surgery.

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REFERENCES

1 **Hirota S**, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577-580 [PMID: 9438854]

2 **Heinrich MC**, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; **299**: 708-710 [PMID: 12522257 DOI: 10.1126/science.1079666]

3 **Hirota S**, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, Kitamura Y. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology* 2003; **125**: 660-667 [PMID: 12949711]

4 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466-1478 [PMID: 17090188]

5 **Miettinen M**, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29**: 52-68 [PMID: 15613856]

6 **Miettinen M**, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; **30**: 1213-1220 [PMID: 10534170]

7 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006; **23**: 70-83 [PMID: 17193820]

8 **Rodriguez SA**, Faigel DO. Endoscopic diagnosis of gastrointestinal stromal cell tumors. *Curr Opin Gastroenterol* 2007; **23**: 539-543 [PMID: 17762560 DOI: 10.1097/MOG.0b013e32829fb39f]

9 **Rossi S**, Gasparotto D, Toffolatti L, Pastrello C, Gallina G, Marzotto A, Sartor C, Barbareschi M, Cantaloni C, Messerini L, Bearzi I, Arrigoni G, Mazzoleni G, Fletcher JA, Casali PG, Talamini R, Maestro R, Dei Tos AP. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. *Am J Surg Pathol* 2010; **34**: 1480-1491 [PMID: 20861712 DOI: 10.1097/PAS.0b013e3181ef7431]

10 **Scherübl H**, Faiss S, Knoefel WT, Wardelmann E. Management of early asymptomatic gastrointestinal stromal tumors of the stomach. *World J Gastrointest Endosc* 2014; **6**: 266-271 [PMID: 25031785 DOI: 10.4253/wjge.v6.i7.266]

11 **Nilsson B**, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. *Cancer* 2005; **103**: 821-829 [PMID: 15648083 DOI: 10.1002/cncr.20862]

12 **Tryggvason G**, Kristmundsson T, Orvar K, Jónasson JG, Magnússon MK, Gíslason HG. Clinical study on gastrointestinal stromal tumors (GIST) in Iceland, 1990-2003. *Dig Dis Sci* 2007; **52**: 2249-2253 [PMID: 17420941 DOI: 10.1007/s10620-006-9248-4]

13 **Abraham SC**, Krasinskas AM, Hofstetter WL, Swisher SG, Wu TT. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. *Am J Surg Pathol* 2007; **31**: 1629-1635 [PMID: 18059218 DOI: 10.1097/PAS.0b013e31806ab2c3]

14 **Agaimy A**, Wünsch PH, Dirnhofer S, Bihl MP, Terracciano LM, Tornillo L. Microscopic gastrointestinal stromal tumors in esophageal and intestinal surgical resection specimens: a clinicopathologic, immunohistochemical, and molecular study of 19 lesions. *Am J Surg Pathol* 2008; **32**: 867-873 [PMID: 18408593 DOI: 10.1097/PAS.0b013e31815c0417]

15 **Agaimy A**, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, Dietmaier W, Hartmann A. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. *Am J Surg Pathol* 2007; **31**: 113-120 [PMID: 17197927 DOI: 10.1097/01.pas.0000213307.05811.f0]

16 **Kawanowa K**, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, Hosoya Y, Nakajima T, Funata N. High incidence of microscopic gastrointestinal stromal tumors in the stomach. *Hum Pathol* 2006; **37**: 1527-1535 [PMID: 16996566]

17 **Hedenbro JL**, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. *Surg Endosc* 1991; **5**: 20-23 [PMID: 1871670]

18 **Arber DA**, Tamayo R, Weiss LM. Paraffin section detection of the c-kit gene product (CD117) in human tissues: value in the diagnosis of mast cell disorders. *Hum Pathol* 1998; **29**: 498-504 [PMID: 9596274]

19 **Aparicio T**, Boige V, Sabourin JC, Crenn P, Ducreux M, Le Cesne A, Bonvalot S. Prognostic factors after surgery of primary resectable gastrointestinal stromal tumours. *Eur J Surg Oncol* 2004; **30**: 1098-1103 [PMID: 15522557 DOI: 10.1016/j.ejso.2004.06.016]

20 **Tashiro T**, Hasegawa T, Omatsu M, Sekine S, Shimoda T, Katai H. Gastrointestinal stromal tumour of the stomach showing lymph node metastases. *Histopathology* 2005; **47**: 438-439 [PMID: 16178904 DOI: 10.1111/j.1365-2559.2005.02133.x]

21 **Tryggvason G**, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer* 2005; **117**: 289-293 [PMID: 15900576 DOI: 10.1002/ijc.21167]

22 **Demetri GD**, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, Corless CL, Debiec-Rychter M, DeMatteo RP, Ettinger DS, Fisher GA, Fletcher CD, Gronchi A, Hohenberger P, Hughes M, Joensuu H, Judson I, Le Cesne A, Maki RG, Morse M, Pappo AS, Pisters PW, Raut CP, Reichardt P, Tyler DS, Van den Abbeele AD, von Mehren M, Wayne JD, Zalcberg J. NCCN Task Force

report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007; **5** Suppl 2: S1-29; quiz S30 [PMID: 17624289]

23 **DeMatteo RP**, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51-58 [PMID: 10636102]

24 **Blay JY**, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP, Emile JF, Gronchi A, Hogendoorn PC, Joensuu H, Le Cesne A, McClure J, Maurel J, Nupponen N, Ray-Coquard I, Reichardt P, Sciot R, Stroobants S, van Glabbeke M, van Oosterom A, Demetri GD. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. *Ann Oncol* 2005; **16**: 566-578 [PMID: 15781488 DOI: 10.1093/annonc/mdi127]

25 **Catena F**, Di Battista M, Fusaroli P, Ansaloni L, Di Scioscio V, Santini D, Pantaleo M, Biasco G, Caletti G, Pinna A. Laparoscopic treatment of gastric GIST: report of 21 cases and literature's review. *J Gastrointest Surg* 2008; **12**: 561-568 [PMID: 18040747 DOI: 10.1007/s11605-007-0416-4]

26 **Bédard EL**, Mamazza J, Schlachta CM, Poulin EC. Laparoscopic resection of gastrointestinal stromal tumors: not all tumors are created equal. *Surg Endosc* 2006; **20**: 500-503 [PMID: 16437270 DOI: 10.1007/s00464-005-0287-2]

27 **Choi SM**, Kim MC, Jung GJ, Kim HH, Kwon HC, Choi SR, Jang JS, Jeong JS. Laparoscopic wedge resection for gastric GIST: long-term follow-up results. *Eur J Surg Oncol* 2007; **33**: 444-447 [PMID: 17174060 DOI: 10.1016/j.ejso.2006.11.003]

28 **Huguet KL**, Rush RM, Tessier DJ, Schlinkert RT, Hinder RA, Grinberg GG, Kendrick ML, Harold KL. Laparoscopic gastric gastrointestinal stromal tumor resection: the mayo clinic experience. *Arch Surg* 2008; **143**: 587-590; discussion 591 [PMID: 18559753 DOI: 10.1001/archsurg.143.6.587]

29 **Lai IR**, Lee WJ, Yu SC. Minimally invasive surgery for gastric stromal cell tumors: intermediate follow-up results. *J Gastrointest Surg* 2006; **10**: 563-566 [PMID: 16627222 DOI: 10.1016/j.gassur.2005.08.028]

30 **Nguyen SQ**, Divino CM, Wang JL, Dikman SH. Laparoscopic management of gastrointestinal stromal tumors. *Surg Endosc* 2006; **20**: 713-716 [PMID: 16502196 DOI: 10.1007/s00464-005-0435-8]

31 **Novitsky YW**, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. *Ann Surg* 2006; **243**: 738-745; discussion 745-747 [PMID: 16772777 DOI: 10.1097/01.sla.0000219739.11758.27]

32 **Rivera RE**, Eagon JC, Soper NJ, Klingensmith ME, Brunt LM. Experience with laparoscopic gastric resection: results and outcomes for 37 cases. *Surg Endosc* 2005; **19**: 1622-1626 [PMID: 16222466 DOI: 10.1007/s00464-005-0290-7]

33 **Nishida T**, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, Otani Y, Shimada Y, Takahashi F, Kubota T. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008; **13**: 416-430 [PMID: 18946752 DOI: 10.1007/s10147-008-0798-7]

34 **Otani Y**, Furukawa T, Yoshida M, Saikawa Y, Wada N, Ueda M, Kubota T, Mukai M, Kameyama K, Sugino Y, Kumai K, Kitajima M. Operative indications for relatively small (2-5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. *Surgery* 2006; **139**: 484-492 [PMID: 16627057 DOI: 10.1016/j.surg.2005.08.011]

35 **Nishimura J**, Nakajima K, Omori T, Takahashi T, Nishitani A, Ito T, Nishida T. Surgical strategy for gastric gastrointestinal stromal tumors: laparoscopic vs. open resection. *Surg Endosc* 2007; **21**: 875-878 [PMID: 17180273 DOI: 10.1007/s00464-006-9065-z]

36 **Wilhelm D**, von Delius S, Burian M, Schneider A, Frimberger E, Meining A, Feussner H. Simultaneous use of laparoscopy and endoscopy for minimally invasive resection of gastric subepithelial masses - analysis of 93 interventions. *World J Surg* 2008; **32**: 1021-1028 [PMID: 18338207 DOI: 10.1007/s00268-008-9492-1]

37 **De Vogelaere K**, Van Loo I, Peters O, Hoorens A, Haentjens P, Delvaux G. Laparoscopic resection of gastric gastrointestinal stromal tumors (GIST) is safe and effective, irrespective of tumor size. *Surg Endosc* 2012; **26**: 2339-2345 [PMID: 22350238 DOI: 10.1007/s00464-012-2186-7]

38 **McCarter MD**, Antonescu CR, Ballman KV, Maki RG, Pisters PW, Demetri GD, Blanke CD, von Mehren M, Brennan MF, McCall L, Ota DM, DeMatteo RP. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. *J Am Coll Surg* 2012; **215**: 53-59; discussion 59-60 [PMID: 22726733 DOI: 10.1016/j.jamcollsurg.2012.05.008]

39 **Catena F**, Di Battista M, Ansaloni L, Pantaleo M, Fusaroli P, Di Scioscio V, Santini D, Nannini M, Saponara M, Ponti G, Persiani R, Delrio P, Coccolini F, Di Saverio S, Biasco G, Lazzareschi D, Pinna A. Microscopic margins of resection influence primary gastrointestinal stromal tumor survival. *Onkologie* 2012; **35**: 645-648 [PMID: 23147540 DOI: 10.1159/000343585]

40 **Lee IL**, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006; **38**: 1024-1028 [PMID: 17058168 DOI: 10.1055/s-2006-944814]

41 **Hwang JC**, Kim JH, Kim JH, Shin SJ, Cheong JY, Lee KM, Yoo BM, Lee KJ, Cho SW. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. *Hepatogastroenterology* 2009; **56**: 1281-1286 [PMID: 19950778]

42 **Białek A**, Wiechowska-Kozłowska A, Pertkiewicz J, Polkowski M, Milkiewicz P, Karpińska K, Ławniczak M, Starzyńska T. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012; **75**: 276-286 [PMID: 22032850 DOI: 10.1016/j.gie.2011.08.029]

43 **Wang Y**, Li Y, Luo H, Yu H. [Efficacy analysis of endoscopic submucosal excavation for gastric gastrointestinal stromal tumors]. *Zhonghua Wei Chang Wai Ke Zazhi* 2014; **17**: 352-355 [PMID: 24760644]

44 **Liu BR**, Song JT, Qu B, Wen JF, Yin JB, Liu W. Endoscopic muscularis dissection for upper gastrointestinal subepithelial tumors originating from the muscularis propria. *Surg Endosc* 2012; **26**: 3141-3148 [PMID: 22580875 DOI: 10.1007/s00464-012-2305-5]

45 **Inoue H**, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Maselli R, Kudo S. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. *Endoscopy* 2012; **44**: 225-230 [PMID: 22354822 DOI: 10.1055/s-0031-1291659]

46 **Gong W**, Xiong Y, Zhi F, Liu S, Wang A, Jiang B. Preliminary experience of endoscopic submucosal tunnel dissection for upper gastrointestinal submucosal tumors. *Endoscopy* 2012; **44**: 231-235 [PMID: 22354823 DOI: 10.1055/s-0031-1291720]

47 **Ye LP**, Zhang Y, Mao XL, Zhu LH, Zhou X, Chen JY. Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. *Surg Endosc* 2014; **28**: 524-530 [PMID: 24013472 DOI: 10.1007/s00464-013-3197-8]

48 **Li QL**, Yao LQ, Zhou PH, Xu MD, Chen SY, Zhong YS, Zhang YQ, Chen WF, Ma LL, Qin WZ. Submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a large study of endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2012; **75**: 1153-1158 [PMID: 22459663 DOI: 10.1016/j.gie.2012.01.037]

49 **Feng Y**, Yu L, Yang S, Li X, Ding J, Chen L, Xu Y, Shi R. Endolumenal endoscopic full-thickness resection of muscularis propria-originating gastric submucosal tumors. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 171-176 [PMID: 24555874 DOI: 10.1089/lap.2013.0370]

50 **Suzuki H**, Ikeda K. Endoscopic mucosal resection and full thickness resection with complete defect closure for early gastrointestinal malignancies. *Endoscopy* 2001; **33**: 437-439 [PMID: 11396763 DOI: 10.1055/s-2001-14269]

51 **Ikeda K**, Mosse CA, Park PO, Fritscher-Ravens A, Bergström M, Mills T, Tajiri H, Swain CP. Endoscopic full-thickness resection: circumferential cutting method. *Gastrointest Endosc* 2006; **64**:

82-89 [PMID: 16813808 DOI: 10.1016/j.gie.2005.12.039]
52 **Zhou PH**, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011; **25**: 2926-2931 [PMID: 21424195 DOI: 10.1007/s00464-011-1644-y]
53 **Izumi Y**, Inoue H, Endo M. Combined endoluminal-intracavitary thoracoscopic enucleation of leiomyoma of the esophagus. A new method. *Surg Endosc* 1996; **10**: 457-458 [PMID: 8661804]
54 **Inoue H**, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, Kudo SE. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). *Surg Oncol Clin N Am* 2012; **21**: 129-140 [PMID: 22098836 DOI: 10.1016/j.soc.2011.09.012]
55 **Hiki N**, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Miki A, Ohyama S, Seto Y. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008; **22**: 1729-1735 [PMID: 18074180 DOI: 10.1007/s00464-007-9696-8]
56 **Tsujimoto H**, Yaguchi Y, Kumano I, Takahata R, Ono S, Hase K. Successful gastric submucosal tumor resection using laparoscopic and endoscopic cooperative surgery. *World J Surg* 2012; **36**: 327-330 [PMID: 22187132 DOI: 10.1007/s00268-011-1387-x]
57 **Abe N**, Takeuchi H, Ooki A, Nagao G, Masaki T, Mori T, Sugiyama M. Recent developments in gastric endoscopic submucosal dissection: towards the era of endoscopic resection of layers deeper than the submucosa. *Dig Endosc* 2013; **25** Suppl 1: 64-70 [PMID: 23368096 DOI: 10.1111/j.1443-1661.2012.01387.x]
58 **Abe N**, Takeuchi H, Yanagida O, Masaki T, Mori T, Sugiyama M, Atomi Y. Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. *Surg Endosc* 2009; **23**: 1908-1913 [PMID: 19184206 DOI: 10.1007/s00464-008-0317-y]
59 **Hoteya S**, Haruta S, Shinohara H, Yamada A, Furuhata T, Yamashita S, Kikuchi D, Mitani T, Ogawa O, Matsui A, Iizuka T, Udagawa H, Kaise M. Feasibility and safety of laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors, including esophagogastric junction tumors. *Dig Endosc* 2014; **26**: 538-544 [PMID: 24355070 DOI: 10.1111/den.12215]
60 **Sakon M**, Takata M, Seki H, Hayashi K, Munakata Y, Tateiwa N. A novel combined laparoscopic-endoscopic cooperative approach for duodenal lesions. *J Laparoendosc Adv Surg Tech A* 2010; **20**: 555-558 [PMID: 20578925 DOI: 10.1089/lap.2009.0392]
61 **Mitsui T**, Niimi K, Yamashita H, Goto O, Aikou S, Hatao F, Wada I, Shimizu N, Fujishiro M, Koike K, Seto Y. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. *Gastric Cancer* 2014; **17**: 594-599 [PMID: 23974429 DOI: 10.1007/s10120-013-0291-5]
62 **Goto O**, Mitsui T, Fujishiro M, Wada I, Shimizu N, Seto Y, Koike K. New method of endoscopic full-thickness resection: a pilot study of non-exposed endoscopic wall-inversion surgery in an ex vivo porcine model. *Gastric Cancer* 2011; **14**: 183-187 [PMID: 21394421 DOI: 10.1007/s10120-011-0014-8]
63 **Dematteo RP**, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **373**: 1097-1104 [PMID: 19303137 DOI: 10.1016/S0140-6736(09)60500-6]
64 **Joensuu H**, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran SE, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, Monge OR, Bono P, Kallio R, Vehtari A, Leinonen M, Alvegård T, Reichardt P. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA* 2012; **307**: 1265-1272 [PMID: 22453568 DOI: 10.1001/jama.2012.347]
65 **Serrano C**, George S. Recent advances in the treatment of gastrointestinal stromal tumors. *Ther Adv Med Oncol* 2014; **6**: 115-127 [PMID: 24790651 DOI: 10.1177/1758834014522491]
66 **Hiki N**. [Feasible technique for laparoscopic wedge resection for gastric submucosal tumor-laparoscopy endoscopy cooperative surgery (LECS)]. *Gan To Kagaku Ryoho* 2011; **38**: 728-732 [PMID: 21566431]

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Techniques and efficacy of flexible endoscopic therapy of Zenker's diverticulum

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Abstract

Zenker's diverticulum (ZD) is an abnormal hypopharyngeal pouch often presenting with dysphagia. Treatment is often sought with invasive surgical management of the diverticulum being the only mode of definitive therapy. Primarily done by an open transcervical approach in the past, nowadays treatment is usually provided by otolaryngologists using a less invasive trans-oral technique with a rigid endoscope. When first described, this method grew into acceptance quickly due to its similar efficacy and vastly improved safety profile compared to the open transcervical approach. However, the main limitation with this approach is that it may not be suitable for all patients. Nonetheless, progress in the field of natural orifice endoscopic surgery over the last 10-20 years has led to the increase in utilization of the flexible endoscope in the treatment of ZD. Primarily performed by interventional gastroenterologists, this approach overcomes the prior limitation of its surgical counterpart and allows adequate visualization of the diverticulum independent of the patient's body habitus. Additionally, it may be performed without the use of general anesthesia and in an outpatient setting, thus further increasing the utility of this modality, especially in elderly patients with other comorbidities. Today, results in more than 600 patients have been described in various published case series using different techniques and devices demonstrating a high percentage of clinical symptom resolution with low rates of adverse events. In this article, we present our experience with flexible endoscopic therapy of Zenker's diverticulum and highlight the endoscopic technique, outcomes and adverse events related to this minimally invasive modality.

Key words: Zenker's diverticulum; Flexible endoscopy; Natural orifice endoscopic surgery; Per-oral endoscopy; Dysphagia; Cricopharyngeus myotomy; Cricopharyngeus septotomy

Core tip: Definitive therapy for Zenker's diverticulum (ZD) typically includes either diverticulectomy or myotomy/

septotomy of the cricopharyngeus muscle. Previously done as an open transcervical approach by surgeons, treatment has now evolved to include a minimally invasive trans-oral approach with flexible endoscopy performed by gastroenterologists. In this article we highlight our experience with flexible endoscopic therapy of ZD at our institution, describe commonly used flexible endoscopic techniques and devices, and assess efficacy and safety data related to this minimally invasive modality.

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INTRODUCTION

Zenker's diverticulum (ZD) is a pharyngeal outpouching caused by increased intraluminal pressure, in conjunction with an area of inherent weakness in the hypopharynx known as the Killian triangle. This area of vulnerability is formed in between two pharyngoesophageal muscles, the inferior pharyngeal constrictor and the cricopharyngeus. Since the original description of the condition by Ludlow[1] and then Zenker von Zeimssen[2]; the pathophysiology that leads to the ZD has been poorly understood. Currently, the mechanism that leads to increase in luminal pressures causing the ZD is thought to be due to poor upper esophageal sphincter (UES) compliance[3,4].

Characteristic symptoms for ZD include dysphagia, which is the presenting symptom in 80%-90% of patients. Additionally, patients may present with cough, dysphonia, malnutrition and weight loss. Occurrence is not usual in patients under the age of 40 years with incidence most prevalent in males in the seventh or eighth decade of life[5]. The diagnosis of ZD is based on clinical and radiographic findings, with dynamic barium esophagram being the confirmatory study[6]. Surgical intervention involving disruption of the cricopharyngeus by myotomy and/or diverticulectomy is the mainstay of treatment. The open trans-cervical approach that was originally described by Wheeler[7] has now evolved after a sentinel paper published by Dohlman and Mattson[8] to a less invasive trans-oral approach using a rigid endoscope. This technique currently performed by otolaryngologists, is the method of choice due to similar efficacy, reduced patient morbidity and overall shorter hospital stay compared to traditional open transcervical surgery[9].

Indeed, all patients who are diagnosed with ZD would ideally undergo endoscopic therapy as the benefits mentioned previously make this a more favorable choice for patients and clinicians. However, as with all surgical procedures there are several pre-interventional considerations. At the crux of these issues are the needs to visualize the diverticulum trans-orally. Several patient indicators including high body mass index and poor neck flexibility predispose the patient to higher risk of adverse events and procedural failure. As such, an open approach is still used in 15% to 68% of cases[5]. Nevertheless, within the past 20 years the trans-oral approach has progressed with the advent use of a flexible endoscope. Currently performed by interventional gastroenterologists/endoscopists, this method helps overcome the prior concerns of visual limitations while still providing a minimal invasive approach to this complex surgical condition. Several variations to this procedure have been explored and published in recent times, though, lacking comprehensive long-term analysis and comparative effectiveness of these various techniques. In this article we highlight our experience with flexible endoscopic therapy of ZD at our institution, describe commonly used flexible endoscopic techniques and devices, and assess efficacy and safety data related to this minimally invasive modality.

THE UNIVERSITY OF FLORIDA (UF) EXPERIENCE

Aims and outcomes

The aim of this study was to assess the efficacy and safety of patients undergoing flexible endoscopic treatment of ZD. Efficacy was defined by: (1) technical success of endoscopic therapy; and (2) improvement in dysphagia score. Safety was characterized by the lack of development of intra-procedural or post-procedural adverse events (AE).

Definitions

Technical success: Procedural technical success was defined as the ability to successfully perform flexible endoscopic cricopharyngeus myotomy.

Dysphagia score: A score range (0-4) was used to quantify dysphagia prior to and after endoscopic treatment[10].

Adverse events: Endoscopic adverse events were assessed based on previously established criteria by the American Society of Gastrointestinal Endoscopy (ASGE)[11].

Methods and techniques

This study was approved by the University of Florida Institutional Review Board (IRB). Our electronic endoscopy database was queried from January 2006 through June 2014 for patients who were referred to a single interventional endoscopist for flexible endoscopic treatment of ZD. Diagnosis of ZD was made with either barium esophagram, computed tomography or direct endoscopic visualization.

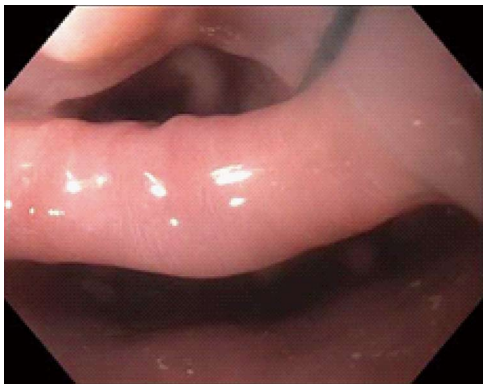

Figure 1 Endoscopic appearance of Zenker's diverticulum (esophageal lumen with guidewire is above the Zenker's diverticulum); note the cricopharyngeus septum separating the Zenker's diverticulum from the esophagus.

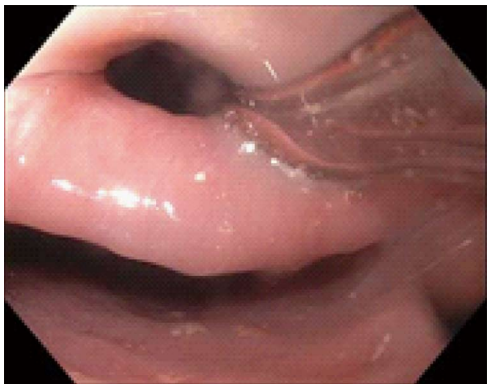

Figure 2 Nasogastric tube in true lumen of the esophagus.

General anesthesia was used per anesthesiologist recommendations and prophylactic antibiotics were typically not given. The procedure was begun after general endoscopic evaluation of the ZD (Figure 1), stomach and duodenum. A nasogastric or orogastric tube (Figure 2) was then placed over a guidewire for improving visualization of the diverticulum and protection of the anterior esophageal wall during myotomy. A needle knife was then used to perform the myotomy (Figure 3) exposing the transverse fibers of the cricopharyngeus. Following the procedure, all patients were then admitted overnight for observation and gradual advance of their diet.

Results

A total of 8 patients [50% male, mean age 72.4 years (range 58-88)] underwent technically successful flexible endoscopic myotomy of their ZD. One endoscopic treatment session was performed per patient and all patients noted improvement in their dysphagia symptoms after therapy. The mean pre-procedure dysphagia score was 2.6 (range 2-4) and post-procedure dysphagia score was 0.4 (range 0-2). There were no AE and mean follow-up time was 5.8 mo (range 0-17). Two patients with mild residual dysphagia did not wish to undergo a repeat procedure or other interventions.

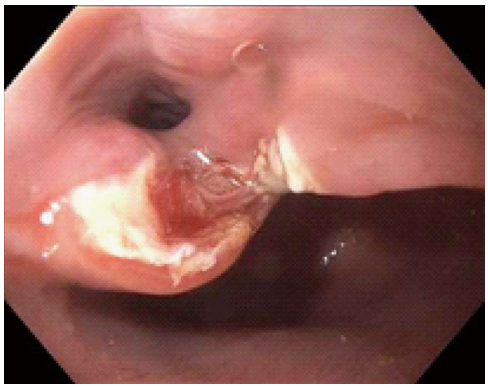

Figure 3 Cricopharyngeus myotomy.

TECHNICAL ASPECTS

Since landmark studies by Mulder[12] and Ishioka[13], the use of flexible endoscopy to treat ZD has come into many centers as an additional minimally invasive modality for management. Described by radiographic and manometric studies by Cook[3], pathogenesis of this abnormality seems to be related to poor UES compliance leading to increase swallowing pressures and in turn a Killian's dehiscence. As such, the mainstay of treatment has been ablation or division of the cricopharyngeus "septum" (cricopharyngeus myotomy or septotomy) and there have been many variations in the way this myotomy is performed. Additionally, most institutions have employed tools aiding to secure and expose the septum such as the diverticuloscope and clear cap assisted devices. Currently, 19 case series/analyses[10,12-29] have been published describing flexible endoscopic therapy in over 600 patients with ZD (Table 1).

Pre-operative assesment

Typically, symptomatic patients undergo barium esophagram and index upper endoscopy for diagnosis of ZD. One of the advantages of flexible endoscopic therapy for ZD is the ability to perform the procedure without general anesthesia in many cases. This allows patients who are not ideal candidates for endotracheal intubation to undergo either moderate sedation (conscious sedation/CS) or deep sedation/monitored anesthesia care (MAC). In published studies (Table 2) where mode of anesthesia was mentioned, greater than half of all patients underwent endoscopic procedures with either CS or MAC, without mention of intraoperative adverse events related to airway compromise. Nevertheless, some authors[26] still insist in using general anesthesia to protect the airway in case of bleeding at the UES and since the improved muscle relaxation provides greater safety assurance when manipulating the endoscope.

Table 1 Published cases for flexible endoscopic therapy of Zenker's diverticulum

Ref.	Total patients (n = 678)	Age (range)	Device for myotomy	Assist device	Pre-procedure dysphagia score	Post-procedure dysphagia score	Clinical symptom resolution rate	Adverse events	Recurrences	Followup (range)
Mulder *et al*[12]	20	Mean 82 (41-100)	FC	None	NA	NA	85%	0%	0	Mean 7 (1-18)
Ishioka *et al*[13]	42	Mean 68 (46-102)	NK	None	NA	NA	93%	5%	7	Mean 38 (12-96)
Hashiba *et al*[14]	47	(58-81)	NK	None	NA	0 or 1	96%	14.9%	0	(0-12)
Mulder *et al*[15]	125	Median 77 (41-100)	APC	None	NA	NA	100%	20%	NA	NA
Sakai *et al*[16]	10	(67-87)	NK	Cap	1.8	0	100%	0%	0	(2-12)
Evrard *et al*[17]	31	Median 78	NK	DS			93%	13%	9	Median 12.5
Costamagna *et al*[18]	28	Median 66 (47-86)	NK	Cap	NA	NA	43%	32%	4	Median 36 (9-60)
Costamagna *et al*[18]	11	Median 70 (63-84)	NK	DS	NA	NA	91%	0%	1	Median 6.5 (3-15)
Rabenstein *et al*[19]	41	Mean 73	APC	Cap	NA	NA	95%	19.5%	5	Mean 16
Christiaens *et al*[10]	21	Median 77.5 (52-89)	FC	Cap	1.5	0	100%	3%	2	Median 22.4
Volgelsang *et al*[20]	31	Median 69 (52-92)	NK	Cap	NA	NA	100%	23%	10	Mean 26
Manner *et al*[21]	8	Mean 66	APC	Cap	NA	NA	NA	37.5%	NA	NA
Tang *et al*[22]	6	Mean 71 (48-91)	NK	Endo Clips	NA	NA	100%	0%	0	NA
Al-Kadi *et al*[23]	18	Mean 80 (68-91)	NK	None	(2-4)	NA	87.5%	5.5%	NA	Mean 27.5
Case *et al*[24]	22	Median 85	NK	None	NA	NA	100%	32%	4	Mean 12.7
Repici *et al*[25]	32	Mean 74.8 (58-92)	HK	Cap	2.96	0.62	NA	6.25%	3	Mean 23.9 (12-48)
Hondo *et al*[26]	5	Median 69.6 (59-83)	HS	DS	2	0.20	NA	0%	0	Mean 1
Huberty *et al*[27]	150	Median 73 (42-94)	NK	DS	1.88	0.34	90.3%	2.2%	31	Median 43 (13-121)
Ramchandani *et al*[28]	3	Mean 79	SB-K	DS	NA	NA	100%	0%	0	NA
Manno *et al*[29]	19	Median 74 (46-84)	IT-K	DS	NA	NA	100%	0%	2	Median 27
Perbtani (current study)	8	72.4	NK	None	2.6	0.4	100%	0%	2	Mean 5.8 (1-17)

NK: Needle knife; IT-K: Insulated tip knife; SB-K: Stag beetle knife; HK: Hook knife; HS: Harmonic scalpel; FC: Forceps coagulation; APC: Argon plasma coagulation; DS: Diverticuloscope; NA: Not available.

Procedural technique

Prior to performing the procedure various steps are essential to ensure safety in performing the myotomy: (1) Placement of a nasogastric (NG) or orogastric (OG) tube is a common practice that has been introduced with two potential benefits: First, it allows enhanced visualization of the esophageal lumen and diverticulum, and secondly it protects the anterior esophageal wall from injury from instruments used during myotomy; (2) Accessories to improve visualization: Sakai *et al*[16] originally described the use of an assist or accessory device during ZD therapy to stabilize and visualize the septum. A transparent oblique-end hood was used at the tip of the endoscope that extended distally. This in turn served to prevent closure of the upper esophageal sphincter thus allowing for better visualization of the tissue bridge between the esophagus and the diverticulum. Similarly, clear mucosectomy caps[19] have been used with similar intentions. In 2003 Evrard *et al*[17] described the use of a soft diverticuloscope as an adjunct that served a similar function as the clear cap device. The diverticuloscope is placed as an overtube on the endoscope and contains two distal flaps that serve to straddle the septum and safeguard the anterior esophageal and posterior diverticular walls. At this point the instrument used to divide the septum is introduced either alongside or through a channel within the endoscope. In review of the published cases, only one study looked at outcomes between accessories. Costamagna *et al*[18] documented lower complication rates and procedural time with the diverticuloscope *vs* using a clear cap. However, it is worth noting that the diverticuloscope is only commercially available in Canada and Europe.

In performing the cricopharyngeus myotomy the optimal instrument for ablation remains debatable. Moreover, due to the lack of prospective comparative trials the device chosen is often dependent on prior training and preference of the endoscopist. The most commonly used device is the needle knife as is our

Table 2 Modes of sedation used *n* (%)

Sedation type	Patients (*n* = 678)
Conscious sedation	352 (52)
Monitored anesthesia care	60 (9)
General anesthesia	77 (11)
Not reported	189 (28)

practice, followed by argon plasma coagulation (APC) and forceps coagulation (Table 3). This is notably different amongst otolaryngologists, where either carbon dioxide laser or a stapler-assisted device is most frequently employed[30]. When using the needle knife the tip of the instrument is placed at the center of the septum where coagulation, blended or alternating current can be used[16,18,20]. The division through the septum occurs in craniocaudal motion, which exposes the transverse fibers of the cricopharyngeal muscle. The incision should not extend past the inferior portion of the diverticulum, as risk for perforation significantly increases. Length of the myotomy has been described safely up to 5-10 mm from the bottom of the ZD[16,26,27] with endoclips placed by some endoscopists[18] distally for prophylaxis against microperforations.

Emerging techniques: Recent advances in natural orifice translumenal endoscopic surgery (NOTES) have given rise to novel myotomy techniques including per oral endoscopic myotomy (POEM)[31]. Similarly, endoscopic submucosal dissection (ESD) techniques have recently been reported[32] to extend its application to aid in cricopharyngeal myotomies. In this small case series, a modified clear cap overtube was created to secure the diverticular wall while indigo carmine solution was injected into the septum. A submucosal bleb or lift was then created which served to increase exposure of the cricopharyngeal muscle fibers and theoretically enabling a safer and more complete myotomy. Although this variation of flexible endoscopic treatment of ZD is in it's infancy, this study highlights the continual innovative modifications being made to optimize clinical outcome, reduce recurrence rate and sidestep technical hurdles faced by its predecessor.

Post-operative care

In the post-operative period patients have been discharged as outpatients after as short as 6 h as long as there were no apparent adverse events[20]. However, in most cases, patients are hospitalized for 24-48 h with gradual progression of their diet 12 h post-operatively. Post-procedural radiologic studies remain institution dependent. The development of perforations is a concern but there is a low sensitivity for detection of microperforations using this method. Additionally, little correlation has been seen between radiographic findings and patient symptoms[6,33]. We endorse imaging only if there is a clinical suspicion for perforation.

Table 3 Devices used for cricopharyngeus myotomy *n* (%)

Device for myotomy	Patients (*n* = 678)
Needle knife	404 (59.6)
APC	174 (25.7)
Forceps coagulation	41 (6)
Hook knife	32 (4.7)
Insulated tip knife	19 (2.9)
Harmonic scalpel	5 (0.7)
Stag beetle knife	3 (0.4)

OUTCOMES

Multiple centers have reported their results of the flexible endoscopic approach to ZD therapy since it's original description in 1995. There have been 19 reported case series that have been published consisting of 670 patients (Table 1). However, due to the subjective manner in which procedural outcome is determined in these series, it is difficult to gauge true objective clinical success. Often, success is based on patient symptoms and not on objective data. Moreover, there are no guidelines or studies that suggest if endoscopic or radiologic surveillance would be beneficial. To improve upon this aspect some centers have instituted using a dysphagia score[10]. The scale ranges from 0-4 as follows: 0: no dysphagia; 1: dysphagia to solids; 2: dysphagia to semi solids; 3: dysphagia to liquids; 4: patient cannot swallow saliva. A score of this manner provides an objective measurement of outcome as is routinely used at our center and in this study as well. In studies where dysphagia score was used, the average pre- and post-treatment dysphagia score was 2.1 (range 1.8-4) and 0.26 (range 0-0.6) respectively. More routinely reported is the clinical resolution rate (CRR). This is commonly described as a symptom improvement either immediately or 2-4 wk post-procedurally. Of the available studies the reported CRR was over 90% (Table 1) and patients with persistent symptoms typically underwent either a repeat procedure or were referred to otolaryngologists for surgical management. Recurrence rate (RR) for symptoms was near 15% from the available data with an average follow-up time of 20 mo. However, follow-up period was not mentioned in nearly a quarter of the reports and is commonly seen as a shortcoming when reporting outcomes for this procedure.

ADVERSE EVENTS

Adverse events (AE) for the flexible endoscopic therapy of ZD have been well reported since first being described. However, due to the lack of standardization there remains heterogeneity of how accounted complications are reported and designated. In the 678 patients that have been reported to undergo the flexible endoscopic procedures, including our current study, 80 patients (11.8%) were reported to

Table 4 Published adverse events after flexible endoscopic therapy of Zenker's diverticulum *n* (%)

Adverse events	80/678 (11.8%)
Micro perforations	52/678 (7.7)
Cervical emphysema	1
Mediastinal emphysema	5
Subcutaneous emphysema	25
Unspecified	21
Macro perforations	4/678 (0.6)
Bleeding	9/678 (1.3)
Infection	12/678 (1.8)
Fever	10
Pneumonia	1
Neck abscess	1
Death	1/678 (0.1)
Adverse events, not otherwise specified	2/678 (0.3)

have AE (Table 4), the most common being micro-perforations, which encompasses greater than half of reported complications. These are described as the patient developing either: cervical, subcutaneous or mediastinal emphysema. Most of these documented by various radiographic studies, had inconsequential medical outcomes and were treated conservatively with or without antibiotics[34]. Macroscopic perforations, the more morbid AE, were only reported in 4 cases. These perforations were seen either during endoscopic visualization or by oral contrast extravasation and were typically managed with endoscopic clipping without any long-term sequelae being reported. Bleeding occurred in 6 of the reported cases, mostly intra-procedural and treated with epinephrine injection, endoclips or electrocautery. Prolonged post-procedural bleeding has only been recorded in 1 case[14] with hemostasis achieved with endoscopic injection of epinephrine. Fever was reported as the most common presentation of infections reported in published cases. Patients were usually treated with antibiotics if specific organ involvement was apparent or for fever lasting more than 24 h. If fever persisted and a focus of infection was not found, then appropriate testing to rule out perforation or mediastinitis is essential[35]. Patient mortality is infrequent, with only one case being reported[15] due to pulmonary embolism. At our institution, similar to previously published series from other centers, we did not encounter any procedural adverse events. However, as mentioned earlier, accurate reporting of AE is likely best achieved in prospective studies using objective predetermined criteria as suggested by the ASGE[11].

CONCLUSION

Flexible endoscopy therapy appears to be a minimally invasive option for the treatment of ZD with several studies showing favorable clinical outcomes and an adequate safety profile. Future efforts should include prospective trials with further standardization of technical aspects, comparison of endoscopic devices and accessories, and report of long-term clinical outcomes with this technique.

REFERENCES

1 **Ludlow A**. A case of obstructed deglutition from a preternatural dilatation of and bag formed in the pharynx. *Medical Observations and Inquiries* 1764; **3**: 85-101

2 **Zenker FA**, von Ziemssen H. Cyclopaedia of the Practice of Medicine, vol 3. London: Low, Marston, Searle, Rivington Pub, 1878: 46-68

3 **Cook IJ**. Clinical disorders of the upper esophageal sphincter. GI Motility Online 2006. Available from: URL: http://www.nature.com/gimo/contents/pt1/full/gimo37.html

4 **Cook IJ**, Gabb M, Panagopoulos V, Jamieson GG, Dodds WJ, Dent J, Shearman DJ. Pharyngeal (Zenker's) diverticulum is a disorder of upper esophageal sphincter opening. *Gastroenterology* 1992; **103**: 1229-1235 [PMID: 1397879]

5 **Law R**, Katzka DA, Baron TH. Zenker's Diverticulum. *Clin Gastroenterol Hepatol* 2014; **12**: 1773-1782; quiz 1773-1782 [PMID: 24055983 DOI: 10.1016/j.cgh.2013.09.016]

6 **Mantsopoulos K**, Psychogios G, Karatzanis A, Künzel J, Lell M, Zenk J, Koch M. Clinical relevance and prognostic value of radiographic findings in Zenker's diverticulum. *Eur Arch Otorhinolaryngol* 2014; **271**: 583-588 [PMID: 23689803 DOI: 10.1007/s00405-013-2562-5]

7 **Wheeler WI**. Pharyngocoele and dilation of the pharynx, with existing diverticulum at lower portion of pharynx lying posterior to the oesophagus, cured by pharyngotomy, being the first of the kind recorded. *Dublin J Med Sci* 1886; **82**: 349-356

8 **Dohlman G**, Mattsson O. The endoscopic operation for hypopharyngeal diverticula: a roentgencinematographic study. *AMA Arch Otolaryngol* 1960; **71**: 744-752 [PMID: 13817253]

9 **Aly A**, Devitt PG, Jamieson GG. Evolution of surgical treatment for pharyngeal pouch. *Br J Surg* 2004; **91**: 657-664 [PMID: 15164432 DOI: 10.1002/bjs.4572]

10 **Christiaens P**, De Roock W, Van Olmen A, Moons V, D' Haens G. Treatment of Zenker's diverticulum through a flexible endoscope with a transparent oblique-end hood attached to the tip and a monopolar forceps. *Endoscopy* 2007; **39**: 137-140 [PMID: 17657700 DOI: 10.1055/s-2006-945118]

11 **Cotton PB**, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, Mergener K, Nemcek A, Petersen BT, Petrini JL, Pike IM, Rabeneck L, Romagnuolo J, Vargo JJ. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010; **71**: 446-454 [PMID: 20189503 DOI: 10.1016/j.gie.2009.10.027]

12 **Mulder CJ**, den Hartog G, Robijn RJ, Thies JE. Flexible endoscopic treatment of Zenker's diverticulum: a new approach. *Endoscopy* 1995; **27**: 438-442 [PMID: 8549441 DOI: 10.1016/S0016-5107(05)80281-0]

13 **Ishioka S**, Sakai P, Maluf Filho F, Melo JM. Endoscopic incision of Zenker's diverticula. *Endoscopy* 1995; **27**: 433-437 [PMID: 8549440]

14 **Hashiba K**, de Paula AL, da Silva JG, Cappellanes CA, Moribe D, Castillo CF, Brasil HA. Endoscopic treatment of Zenker's diverticulum. *Gastrointest Endosc* 1999; **49**: 93-97 [PMID: 9869730]

15 **Mulder CJ**. Zapping Zenker's diverticulum: gastroscopic treatment. *Can J Gastroenterol* 1999; **13**: 405-407 [PMID: 10377471]

16 **Sakai P**, Ishioka S, Maluf-Filho F, Chaves D, Moura EG. Endoscopic treatment of Zenker's diverticulum with an oblique-end hood attached to the endoscope. *Gastrointest Endosc* 2001; **54**: 760-763 [PMID: 11726857]

17 **Evrard S**, Le Moine O, Hassid S, Devière J. Zenker's diverticulum: a new endoscopic treatment with a soft diverticuloscope. *Gastrointest Endosc* 2003; **58**: 116-120 [PMID: 12838237]

18 **Costamagna G**, Iacopini F, Tringali A, Marchese M, Spada C, Familiari P, Mutignani M, Bella A. Flexible endoscopic Zenker's

diverticulotomy: cap-assisted technique vs. diverticuloscope-assisted technique. *Endoscopy* 2007; **39**: 146-152 [PMID: 17327973 DOI: 10.1055/s-2007-966140]

19 **Rabenstein T**, May A, Michel J, Manner H, Pech O, Gossner L, Ell C. Argon plasma coagulation for flexible endoscopic Zenker's diverticulotomy. *Endoscopy* 2007; **39**: 141-145 [PMID: 17327972 DOI: 10.1055/s-2007-966164]

20 **Vogelsang A**, Preiss C, Neuhaus H, Schumacher B. Endotherapy of Zenker's diverticulum using the needle-knife technique: long-term follow-up. *Endoscopy* 2007; **39**: 131-136 [PMID: 17041841 DOI: 10.1055/s-2006-944657]

21 **Manner H**, May A, Rabenstein T, Pech O, Nachbar L, Enderle MD, Gossner L, Ell C. Prospective evaluation of a new high-power argon plasma coagulation system (hp-APC) in therapeutic gastrointestinal endoscopy. *Scand J Gastroenterol* 2007; **42**: 397-405 [PMID: 17354121 DOI: 10.1080/00365520600898130]

22 **Tang SJ**, Jazrawi SF, Chen E, Tang L, Myers LL. Flexible endoscopic clip-assisted Zenker's diverticulotomy: the first case series (with videos). *Laryngoscope* 2008; **118**: 1199-1205 [PMID: 18401278 DOI: 10.1097/MLG.0b013e31816e2eee]

23 **Al-Kadi AS**, Maghrabi AA, Thomson D, Gillman LM, Dhalla S. Endoscopic treatment of Zenker diverticulum: results of a 7-year experience. *J Am Coll Surg* 2010; **211**: 239-243 [PMID: 20670862 DOI: 10.1016/j.jamcollsurg.2010.04.011]

24 **Case DJ**, Baron TH. Flexible endoscopic management of Zenker diverticulum: the Mayo Clinic experience. *Mayo Clin Proc* 2010; **85**: 719-722 [PMID: 20675509 DOI: 10.4065/mcp.2009.0663]

25 **Repici A**, Pagano N, Romeo F, Danese S, Arosio M, Rando G, Strangio G, Carlino A, Malesci A. Endoscopic flexible treatment of Zenker's diverticulum: a modification of the needle-knife technique. *Endoscopy* 2010; **42**: 532-535 [PMID: 20593330 DOI: 10.1016/j.gie.2012.12.008]

26 **Hondo FY**, Maluf-Filho F, Giordano-Nappi JH, Neves CZ, Cecconello I, Sakai P. Endoscopic treatment of Zenker's diverticulum by harmonic scalpel. *Gastrointest Endosc* 2011; **74**: 666-671 [PMID: 21872715 DOI: 10.1016/j.gie.2011.05.007]

27 **Huberty V**, El Bacha S, Blero D, Le Moine O, Hassid S, Devière J. Endoscopic treatment for Zenker's diverticulum: long-term results (with video). *Gastrointest Endosc* 2013; **77**: 701-707 [PMID: 23394840]

28 **Ramchandani M**, Nageshwar Reddy D. New endoscopic "scissors" to treat Zenker's diverticulum (with video). *Gastrointest Endosc* 2013; **78**: 645-648 [PMID: 23849817 DOI: 10.1016/j.gie.2013.06.003]

29 **Manno M**, Manta R, Caruso A, Bertani H, Mirante VG, Osja E, Bassotti G, Conigliaro R. Alternative endoscopic treatment of Zenker's diverticulum: a case series (with video). *Gastrointest Endosc* 2014; **79**: 168-170 [PMID: 23987574 DOI: 10.1016/j.gie.2013.07.012]

30 **Parker NP**, Misono S. Carbon dioxide laser versus stapler-assisted endoscopic Zenker's diverticulotomy: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2014; **150**: 750-753 [PMID: 24496741 DOI: 10.1177/0194599814521554]

31 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937]

32 **Kedia P**, Fukami N, Kumta NA, Kahaleh M, Sharaiha RZ. A novel method to perform endoscopic myotomy for Zenker's diverticulum using submucosal dissection techniques. *Endoscopy* 2014; **46**: 1119-1121 [PMID: 25325681 DOI: 10.1055/s-0034-1377967]

33 **Witterick IJ**, Gullane PJ, Yeung E. Outcome analysis of Zenker's diverticulectomy and cricopharyngeal myotomy. *Head Neck* 1995; **17**: 382-388 [PMID: 8522438 DOI: 10.1002/hed.2880170504]

34 **Dzeletovic I**, Ekbom DC, Baron TH. Flexible endoscopic and surgical management of Zenker's diverticulum. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 449-465; quiz 466 [PMID: 22928898 DOI: 10.1586/egh.12.25]

35 **Ferreira LE**, Simmons DT, Baron TH. Zenker's diverticula: pathophysiology, clinical presentation, and flexible endoscopic management. *Dis Esophagus* 2008; **21**: 1-8 [PMID: 18197932 DOI: 10.1111/j.1442-2050.2007.00795.x]

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MINIREVIEWS

Endosonography in the diagnosis and management of pancreatic cysts

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Abstract

Rapid advances in radiologic technology and increased cross-sectional imaging have led to a sharp rise in incidental discoveries of pancreatic cystic lesions. These cystic lesions include non-neoplastic cysts with no risk of malignancy, neoplastic non-mucinous serous cystadenomas with little or no risk of malignancy, as well as neoplastic mucinous cysts and solid pseudopapillary neoplasms both with varying risk of malignancy. Accurate diagnosis is imperative as management is guided by symptoms and risk of malignancy. Endoscopic ultrasound (EUS) allows high resolution evaluation of cyst morphology and precise guidance for fine needle aspiration (FNA) of cyst fluid for cytological, chemical and molecular analysis. Initially, clinical evaluation and radiologic imaging, preferably with magnetic resonance imaging of the pancreas and magnetic resonance cholangiopancreatography, are performed. In asymptomatic patients where diagnosis is unclear and malignant risk is indeterminate, EUS-FNA should be used to confirm the presence or absence of high-risk features, differentiate mucinous from non-mucinous lesions, and diagnose malignancy. After analyzing the cyst fluid for viscosity, cyst fluid carcinoembryonic antigen, amylase, and cyst wall cytology should be obtained. DNA analysis may add useful information in diagnosing mucinous cysts when the previous studies are indeterminate. New molecular biomarkers are being investigated to improve diagnostic capabilities and management decisions in these challenging cystic lesions. Current guidelines recommend surgical pancreatic resection as the standard of care for symptomatic cysts and those with high-risk features associated with malignancy. EUS-guided cyst ablation is a promising minimally invasive, relatively low-risk alternative to both surgery and surveillance.

Key words: Endoscopic ultrasound; Pancreatic cyst; Serous cystadenoma; Intraductal papillary mucinous neoplasms; Mucinous cystic neoplasm; Solid pseudopapillary neoplasms; diagnosis; Management; Ablation

Core tip: Endoscopic ultrasound with fine needle aspiration (EUS-FNA) is an important and safe diagnostic tool in pancreatic cystic lesions to help

diagnose malignancy, identify features concerning for malignancy, and differentiate mucinous from non-mucinous cysts. More recently EUS-guided pancreatic cyst ablation may offer a minimally invasive and safer alternative to surgical resection for carefully selected pancreatic cysts.

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INTRODUCTION

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has revolutionized diagnosis, and more recently treatment, of a variety of gastrointestinal conditions accurately and safely. This includes the seemingly ubiquitous pancreatic cystic lesion. The rapid advancement and widespread use of cross-sectional imaging has resulted in more incidentally discovered pancreatic cysts. Recent studies from the United states have estimated an overall prevalence of 2.5%[1]. Pancreatic cysts may be seen in as many as 14%-20% of magnetic resonance imaging (MRI) studies[2,3] and in 3% of computed tomography (CT) scans[4]. The prevalence of these incidental cystic lesions is directly correlated to increasing age[5]. Internationally, studies have shown steadily increasing rates of detection of pancreatic cysts over the years[6] and, specifically, intraductal papillary mucinous neoplasms (IPMN)[7]. In addition to increased frequency, the median size of these incidentally detected lesions has decreased by about half from 3 cm to 1.5 cm over 12 years in a Korean study[6] and from 4 cm to 2 cm over 5 years in a study from the United States[8].

This trend of increased discovery of pancreatic cysts is particularly important because specific types of pancreatic cystic lesions have varying potential for malignant transformation[9]. A study of a large national database estimated the overall prevalence of malignant cysts as 33 in 100000[1], and recent natural history studies have estimated 1.3%-3.3%[6,8]. Pancreatic cysts can generally be classified as non-neoplastic, neoplastic and necrosis of solid tumors. Non-neoplastic cysts have no malignant potential; these include pseudocysts, retention cysts, mucinous non-neoplastic cysts, lymphoepithelial cysts and benign epithelial cysts. Two-thirds of pancreatic cysts are cystic neoplasms (Table 1); these include mucinous cysts [mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN)], non-mucinous cysts [serous cystadenoma (SCA)] and solid pseudopapillary neoplasms (SPEN). Mucinous cysts and SPENs are considered premalignant or may harbor malignancy. There is further variability in malignant potential among the premalignant mucinous subtypes [MCN, branch duct (BD)-IPMN, main duct (MD)-IPMN and mixed/combined IPMN]. Non-mucinous SCAs have little to no malignant potential. Consequently, these different types of cystic lesions require a range of different management strategies, from monitoring to surgical resection, depending on the risk of malignant transformation[10,11]. Therefore, accurate diagnosis is of the utmost importance.

Initial diagnostic testing usually focuses on radiologic imaging. Following incidental identification of a pancreatic cyst, MRI of the pancreas with magnetic resonance cholangiopancreatography (MRCP) is recommended[12]. If MRI/MRCP cannot be performed, a pancreatic protocol multidetector (MD) CT should be obtained. MRI/MRCP is preferable as it is better able to evaluate septa, nodules, main pancreatic duct involvement, branch duct involvement, communication with the main pancreatic duct and cyst contents/debris; and is 79%-82% accurate in identifying mucinous cysts[13-16]. Both CT and MRI predict the presence of malignancy in pancreatic cysts with 73%-79% accuracy[17]. A recent retrospective study of resected pancreatic cysts noted MRI was 100% accurate for diagnosing mucinous and malignant cysts, although sample size was small (4-7 patients), while CT was 53%-56% accurate[18].

ROLE OF EUS IN DIAGNOSIS OF PANCREATIC CYSTS

Clinical evaluation, MDCT and MRI may be sufficient to make the diagnosis and guide management when certain pathognomonic and/or characteristic features are present[9-11,19]. While individual cyst types do have characteristic morphologic features, their actual appearance on imaging studies can be very similar[20,21]. Clinical and radiologic findings are often indeterminate, making diagnosis and estimating risk of malignancy difficult. A recent study examined the diagnostic utility of EUS and EUS-FNA beyond that of radiology. EUS with or without cyst fluid aspirate analysis [cytology, amylase and carcinoembryonic antigen (CEA)] was more sensitive (76%) than CT or MRI (48% and 34%) for differentiating neoplastic from non-neoplastic cysts[22]. While these results indicate EUS may be useful in identifying neoplastic cysts, the accuracy of radiologic imaging in this study was far lower than has been demonstrated by others. This study also only applies to resected cysts, which may bias in favor of EUS.

Following initial evaluation it is necessary to decide if a patient requires further diagnostic testing by EUS/EUS-FNA, radiologic surveillance or surgical resection. Patients with symptomatic pancreatic cysts (*e.g.,* pancreatitis) should be evaluated for surgery. In addition, the 2012 International Association of Pancreatology (IAP) guidelines for mucinous cysts

Table 1 Characteristics of common pancreatic cystic lesions

Characteristic	Pseudocyst	SCA	MCN	MD-IPMN[1]	BD-IPMN[1]	SPEN
Male:female	1:1	1:4	Nearly all female	2:1	2:1	1:4
Age (yr)	40-70	60-80	30-50	60-80	60-80	20-30
Location	Any	Any	Body, tail (90%)	Any (head and uncinate 50%)	Any (head and uncinate 50%)	Body, tail (60%)
Imaging features	Unilocular, thick or thin walled	Multilocular, lobulated. Typically microcystic appearance. Central scar	Unilocular, smooth and encapsulated. Septations and peripheral calcifications possible	Diffuse or focal main duct dilation. Fish-mouth papilla with visible mucus	Dilated side branches. Lobular with septations. "Bunch of grapes" appearance	Unilocular, encapsulated with solid and cystic structure. Hemorrhagic components
Communication with main duct	Variable	None	None	Yes	Yes	None
Cytology	Cyst contents	Cuboidal cells. Glycogen (+), PAS (+) and hemosiderin-laden macrophages	Columnar cells. Atypia varies. Mucin (+)	Columnar cells. Atypia varies. Mucin (+)	Columnar cells. Atypia varies. Mucin (+)	Branching papillae and fibrovascular stroma. Vimentin (+), chromogranin (-) and keratin (-)
Amylase (U/L)	> 250	< 250	< 250	> 250	> 250	N/A
CEA (ng/mL)	< 5	< 5	> 192	> 192	> 192	N/A
KRAS mutation	None	None	Yes	Yes	Yes	N/A
Malignant potential	None	Very rare	Yes (6%-27%)	Yes (40%-70%)	Yes (15%-20%)	Yes (2%-15%)
Morphological predictors of malignancy	None	None	> 6 cm, solid component, peripheral nodules or calcifications	Main duct ⩾ 8 mm, solid component, nodules	⩾ 3 cm, solid component, nodules, main duct ⩾ 1 cm, and suspicious/ malignant cytology	None

[1]Mixed IPMN have features of both MD and BD-IPMN. SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; MD-IPMN: Main duct intraductal papillary mucinous neoplasm; BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; SPEN: Solid pseudopapillary neoplasm; PAS: Periodic acid-Schiff stain; CEA: Carcinoembryonic antigen.

recommends that patients with these "high risk stigmata" for malignancy should undergo surgical evaluation: obstructive jaundice with a cyst located in the pancreatic head, a solid component with post-contrast enhancement, or a main pancreatic duct diameter ⩾ 10 mm[23]. Patients suspected of having SPENs should also be referred for surgery. Among asymptomatic patients with incidental cysts, a decision analysis study compared three management strategies: radiologic follow-up, surgery for all surgical candidates and an EUS-directed approach. The most cost-effective approach was to use EUS-FNA to guide the decision to manage the cystic lesion with radiologic follow-up or surgery[24].

The suggested approach to asymptomatic patients with incidentally discovered cysts is based on cyst size and the presence of features concerning for malignancy (solid component, mural nodule and main pancreatic duct ⩾ 1 cm) (Figure 1)[10]. Patients with cysts < 1 cm and no concerning features can be followed with radiologic imaging unless any change (*e.g.,* increased size) is detected, at which point EUS-FNA is warranted. In patients with cysts > 1 cm, further investigation by EUS-FNA would be advised to rule out the presence of concerning features and determine if the cyst is mucinous. In a recent retrospective study of resected cysts > 3 cm, EUS-FNA with cytology and cyst fluid analysis correctly identified mucinous and non-mucinous lesions in 88% of cases[18]. Even in patients with high risk features or imaging consistent with SPEN where surgery is indicated, evaluation by EUS-FNA and/or endoscopic retrograde pancreatography may be helpful in confirming risk of malignancy (or malignancy) prior to resection, particularly if the patient is a poor or reluctant surgical candidate. The same study of resected cysts > 3 cm found that 65% of these cysts were benign and that cytology, cyst fluid CEA and amylase had a negative predictive value of 94.1% for malignancy, which may allow conservative management in high-risk surgical candidates[18].

Among the mucinous lesions, MCN and IPMN can often be difficult to distinguish. In cases where these two types are lesions are suspected, the 2012 IAP guidelines recommend EUS in patients who present with pancreatitis or "worrisome features" (size ⩾ 3 cm, thick enhancing wall, non-enhancing nodule, main pancreatic duct diameter 5-9 mm, abrupt change in duct diameter with distal gland atrophy and lymphadenopathy)[23]. In these cases EUS should be used to confirm nodules, main duct involvement and cytological atypia with FNA. Surgery is indicated if any of these three features are confirmed. In cases where these features are absent, close surveillance of cysts > 2 cm by EUS and MRI is recommended. Alternatively, surgery may be considered in a young otherwise healthy person who would require prolonged monitoring. When initial EUS is inconclusive, cysts should be closely monitored with EUS and MRI[23].

EUS MORPHOLOGY

EUS is a minimally invasive procedure allowing high

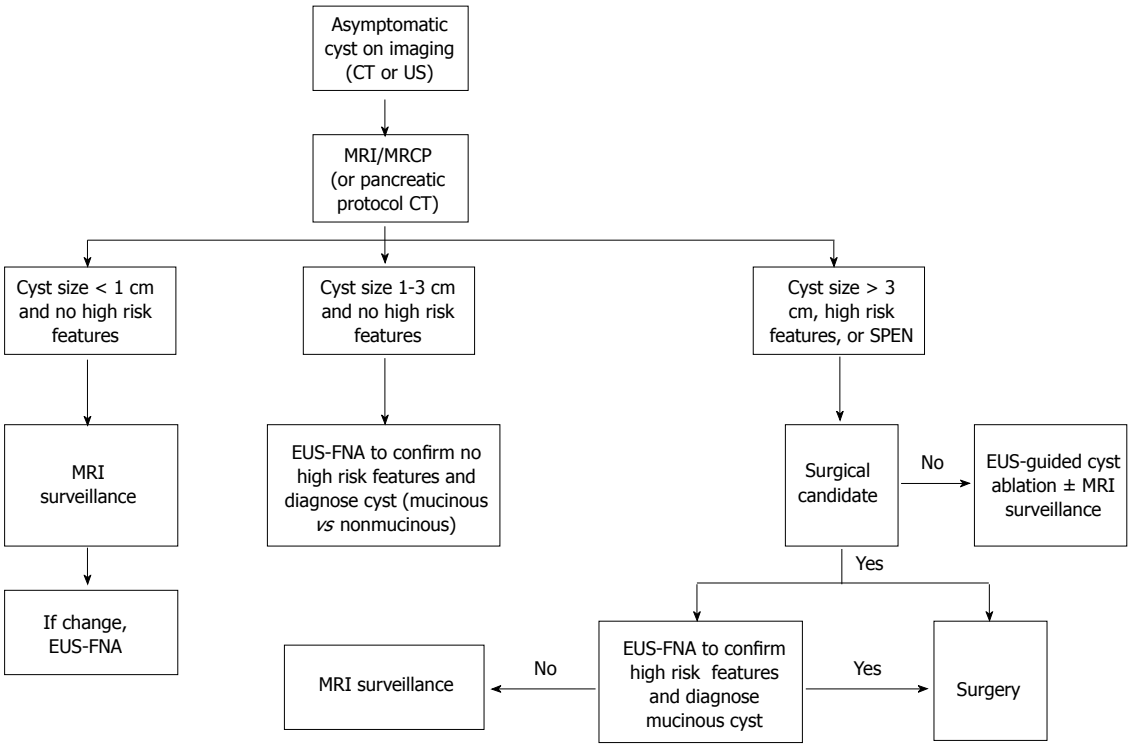

Figure 1 Approach using endoscopic ultrasound in the diagnosis of asymptomatic pancreatic cystic lesions. CT: Computed tomography; EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; MRCP: Magnetic resonance cholangiography; MRI: Magnetic resonance imaging; SPEN: Solid pseudopapillary neoplasm; US: Ultrasound.

Table 2 Endoscopic ultrasound features suggestive of mucinous or malignant cysts

EUS Feature	Type of cyst	Concerning for increased risk of malignancy
Size	-	> 3 cm
Shape	Smooth unilocular: pseudocyst or MCN	-
	Lobular, multilocular: SCA or BD-IPMN	
Number of cysts	Multiple: BD-IPMN	-
Calcifications	Central scar: pathognomonic for SCA	Peripheral calcification in MCN
	Peripheral calcification: pseudocyst, SPEN, MCN	
Cyst wall	Thick: pseudocyst, cystic neuroendocrine, MCN, SPEN	Thick
Septa	-	Thick
Nodule	-	Presence
Solid mass	-	Presence
Debris	Pseudocyst	-
Pancreatic duct diameter	Dilated > 5 mm: MD-IPMN or mixed IPMN	Dilated > 8-10 mm
Communication with pancreatic duct	IPMN, pseudocyst	-

EUS: Endoscopic ultrasound; MCN: Mucinous cystic neoplasm; SCA: Serous cystadenoma; BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; MD-IPMN: Main duct intraductal papillary mucinous neoplasm; SPEN: Solid pseudopapillary neoplasm; IPMN: Intraductal papillary mucinous neoplasm.

resolution diagnostic evaluation of the pancreatic parenchyma and ductal system. A linear echoendoscope should be used to evaluate pancreatic cystic lesions as FNA may be performed. EUS is particularly valuable in assessing diagnostic features and potential predictors of malignancy, including size, shape (lobular *vs* smooth contour), number of cysts, calcifications, cyst wall structure (thick *vs* thin wall), septa, nodules, solid masses associated with the cyst, pancreatic duct diameter, communication with the pancreatic duct, and lymphadenopathy (Table 2, Figures 2A-G). In a study of 50 patients EUS was found to be comparable to MRI in its sensitivity for identifying septa (77.8%), mural nodules (58.3%), main duct dilation (85.7%) and communication with the pancreatic duct (88.9%)[17].

Nodules are an important predictor of malignancy, but may be difficult to distinguish from mucus. Mucus appears as a hypoechoic lesion relative to adjacent tissue with a smooth, hyperechoic rim (Figure 2H). On the other hand, nodules are iso- or hyperechoic compared to adjacent tissue without a hyperechoic rim or smooth edge (Figure 2I). During EUS, rotating the patient and trying to move the lesion with a FNA needle can also help to differentiate mucus from a

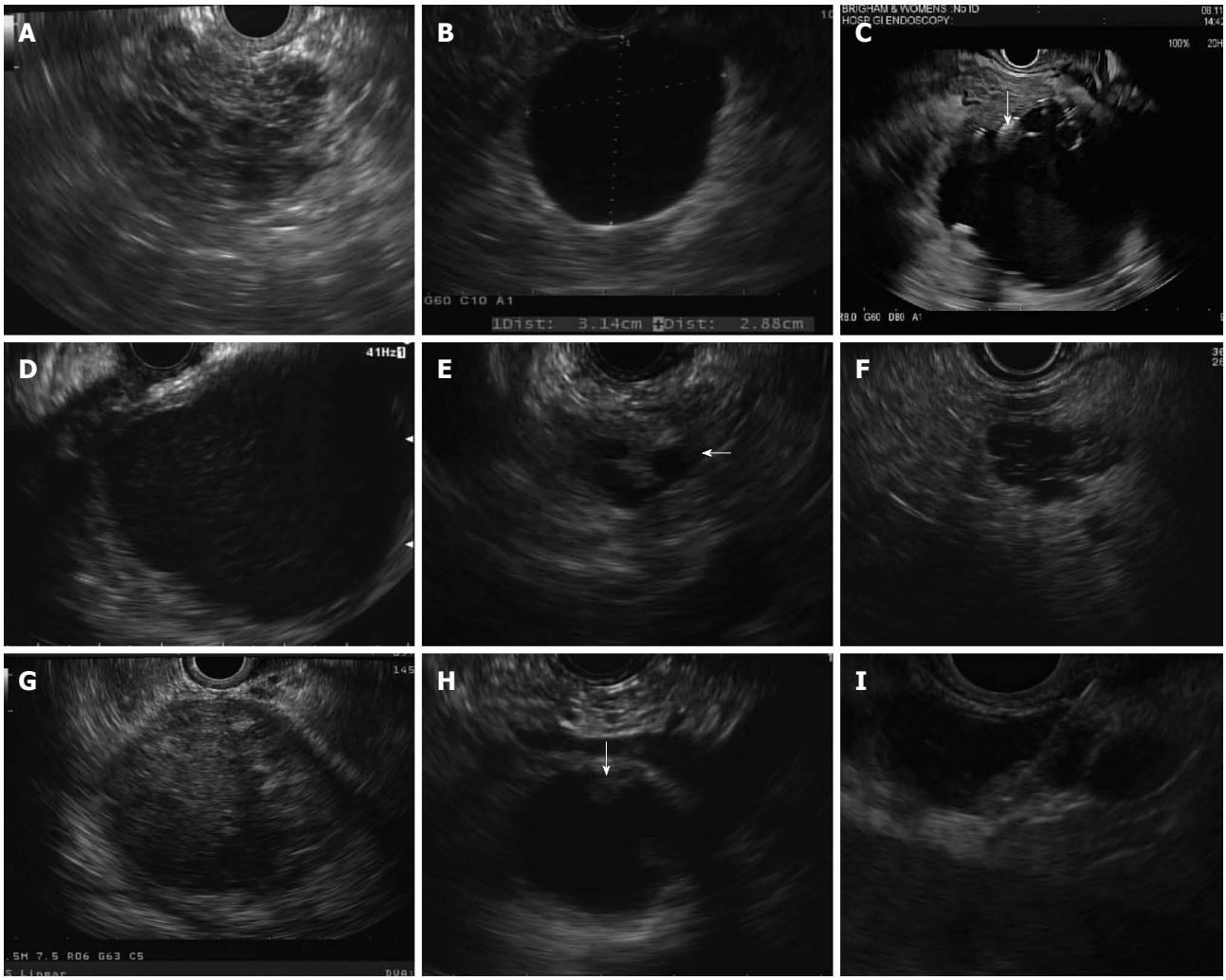

Figure 2 Endoscopic ultrasound imaging. A: A lobular microcystic lesion consistent with serous cystadenoma; B: A smooth, unilocular, thin walled cyst consistent with mucinous cystic neoplasm; C: A cyst with peripheral calcification (arrow) and debris layering at the bottom of the cyst consistent with pseudocyst; D: A thick walled cyst filled with debris representing walled-off pancreatic necrosis; E: A cyst communicating with a nondilated main pancreatic duct (arrow) representing branch duct intraductal papillary mucinous neoplasm; F: A multiseptated lobular cyst appearing like a "cluster of grapes" consistent with branch duct intraductal papillary mucinous neoplasm; G: A well-defined heterogeneous mass-like lesion with hyperechoic foci and small anechoic focus diagnosed as solid pseudopapillary neoplasm on cytology; H: A unilocular cyst with mucus (arrow) appearing hypoechoic relative to the adjacent pancreatic parenchyma with a smooth hyperechoic rim; I: Endoscopic ultrasound-guided fine needle aspiration of a nodule which appears isoechoic with pancreatic parenchyma without a hyperechoic rim within a dilated main pancreatic duct. Cytology showed adenocarcinoma.

nodule. A pathology-based study of MCN and BD-IPMN confirmed the modest diagnostic accuracy of EUS for a nodule (57%)[25]. However, after training endosonographers in the above EUS criteria for differentiating a nodule from mucus, accuracy improved to 79%. The sensitivity and specificity of EUS (75% and 83%) were superior to CT (24% and 100%) for nodules[25], and likely surpasses diagnostic yield of MRI as well when using these defined criteria. In addition, EUS is superior to CT and potentially MRI for detecting small pancreatic masses[26,27]. EUS demonstrated 98% sensitivity compared with 86% for MDCT for identifying pancreatic masses[26]. Data comparing EUS and MRI is limited with an older study supporting higher sensitivity for EUS. More studies are needed using the newer MRI machines.

A recent multicenter study from Korea examined 84 resected BD-IPMNs in order to evaluate EUS predictors of malignancy in BD-IPMNs[28]. An EUS scoring system (0-10) was developed in which points were assigned based on cyst size, mural nodules, pancreatic duct dilation, thick septa and the characteristic "patulous" papilla[28]. This scoring system was found to have an overall area under the curve of 0.944 with 75% sensitivity and 94% specificity for malignant BD-IPMN using an EUS score cutoff of $\geqslant$ 7. In their data, this EUS score was more specific than the 2012 IAP criteria (16%) and mural nodules alone (46%), but less sensitive (2012 IAP criteria 100% and mural nodules 94%).

Despite the utility of EUS imaging in diagnostic evaluation and estimating malignant potential of pancreatic cysts, EUS alone is not adequate for diagnosis of pancreatic cysts. A multicenter trial

Table 3 Endoscopic ultrasound-fine needle aspiration cyst fluid analysis

Cyst fluid marker	Type of cyst	Sensitivity	Specificity
CEA < 5 ng/mL	SCA, pseudocyst, neuroendocrine tumor	54%	94%
CEA >192 ng/mL	Mucinous cyst (MCN or IPMN)	73%	84%
CEA > 800 ng/mL	Mucinous cyst (MCN or IPMN)	98%	48%
Amylase < 250 U/L	Excludes pseudocyst	44%	98%
KRAS mutation + LOH	Malignant cyst	37%	96%
KRAS mutation	Mucinous cyst (MCN or IPMN)	54%	100%

CEA: Carcinoembryonic antigen; SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; LOH: Loss of heterozygosity.

of 341 patients found EUS morphology to be only 56% sensitive and 45% specific (51% accurate) in distinguishing mucinous from non-mucinous cysts[29]. Furthermore, EUS performance is highly operator dependent. Agreement among expert endosonographers (performed > 1000 pancreas EUS) was better than semi-experts (performed 50-200 pancreas EUS) in a Dutch study[30]. However, even among expert endosonographers, interobserver agreement was fair to moderate in distinguishing mucinous and non-mucinous cysts [intraclass correlation coefficient (ICC) = 0.43][30,31]. There was good agreement among experts for nodules (ICC 0.65); moderate for solid component (ICC = 0.52) and communication between cyst and main duct (ICC = 0.44); and fair for suspected malignancy (ICC = 0.27)[30]. An earlier study of 31 cases found only fair interobserver agreement (κ = 0.24) among 8 endosonographers at tertiary care referral centers for distinguishing neoplastic from non-neoplastic lesions by EUS, with accuracy ranging from 40%-93%[31].

EUS-FNA

Due to the limitations of imaging alone, diagnosing pancreatic cysts requires a combination of diagnostic imaging and cyst fluid analysis. Under EUS-guidance, FNA can safely obtain cyst fluid for cytologic and molecular analysis[32]. Cysts should be at least 1 cm in size to obtain sufficient fluid for analyses. The general technique of EUS-FNA of pancreatic cysts is similar to FNA of solid lesions with a few differences to minimize complications. Cyst fluid is usually aspirated with a single pass using a 22 or 25-gauge aspiration needle with the goal of completely collapsing the cyst. Occasionally 19-gauge aspiration needles can be advanced into larger cysts with thick fluid although these larger needles are difficult to use in the pancreatic head or uncinate process. A dose of prophylactic intravenous antibiotics (usually fluoroquinolone) is recommended followed by 3 d of oral antibiotic to prevent infection from cyst aspiration[33].

Before sending the cyst fluid for testing, visual inspection of the fluid may offer diagnostic clues. Fluid viscosity may be evaluated by the "string sign": a drop of fluid is placed between the thumb and first finger and slowly pulled apart. If the fluid stretches out at least 3.5 mm, this is consistent with a mucinous cyst[34]. SCAs typically have thin, serosanguinous or frankly bloody fluid while pseudocyst fluid appears cola-colored and fluid from lymphangiomas may look like milk.

Cyst fluid aspirates are often virtually acellular and consequently cytology has generally limited utility (< 50% sensitive) in diagnosing mucinous lesions[29,35,36]. Exceptions include cyst fluid cytology of cystic neuroendocrine tumors, SPENs, and lymphangiomas where diagnostic yield may be higher[37-41]. Specifically targeting the cyst wall during aspiration has been shown to increase the diagnostic yield of cytology for mucinous lesions by 29% compared to fluid cytology[42]. This is a simple technique whereupon after cyst fluid is aspirated and the cyst wall collapsed, the needle is advanced back and forth through the wall several times, and the tissue sent for cytology. A core biopsy needle may increase diagnostic yield from pancreatic cysts without increased complications. A study of 60 cysts biopsied using the 22 gauge Procore Echotip biopsy needle (Cook Medical, Ireland) reported a 65% sample adequacy rate and 100% concordance between biopsy diagnosis and surgical pathology (available in 28% of the patients) with only minor complications in 3.3% of patients[43]. Further studies are needed to compare fine needle biopsy with fine needle aspiration. In order to further improve diagnostic yield and accuracy, FNA should also target mural nodules and/or solid components when present.

Chemical analysis of cyst fluid usually measures carcinoembryonic antigen (CEA) and amylase concentrations (Table 3). Amylase below 250 U/L can rule out a pseudocyst with 98% specificity[44]. Usually, although not always, amylase is lower in SCA. Typically amylase levels are higher in IPMN than MCN although they can be similar as well. CEA is the main biomarker used to determine if a cyst is mucinous. CEA > 192 ng/mL is 73% sensitive, 84% specific, and 79% accurate for mucinous lesions from the classic study by Brugge *et al*[29]. The exact threshold used for diagnosing mucinous cysts remains debated with higher levels yielding greater specificity but lower sensitivity. For example, CEA > 800 ng/mL is 98% specific but only 48% sensitive for mucinous cysts, which means that cysts with elevated CEA are almost always mucinous while many mucinous cysts with CEA < 800 will be missed[44].

Conversely, low CEA < 5 ng/mL is 95% specific for SCA, pseudocyst, or neuroendocrine tumor[44]. Cyst fluid CEA is not predictive of malignancy[45]. It is important to note that currently available assays are validated for measuring serum, but not cyst fluid, CEA concentrations. Consequently, there is as much as 85% variation in mean cyst fluid CEA concentrations among the various assays[46].

Molecular analysis of aspirated cyst fluid for DNA mutations may help to distinguish mucinous from non-mucinous cyts. A study including 142 surgically resected cysts found that KRAS mutation was 54% sensitive and 100% specific for mucinous cysts[47]. Specifically, KRAS mutations were 67% sensitive for IPMNs but only 14% sensitive for MCN. Using a combination of CEA and KRAS improved sensitivity for mucinous lesions to 83% but specificity dropped to 85%[47]. On the other hand, a smaller study of 48 resected cysts reported that combining KRAS, CEA and cytology did not improve accuracy compared to CEA and cytology or KRAS alone[48]. Two or more loss of heterozygosity (LOH) mutations and DNA quantity > 40 ng/μL were each less than 11% sensitive for mucinous cysts. However, the presence of any molecular changes (KRAS, LOH or elevated DNA quantity) was over 90% specific for mucinous cysts. Consequently, the utility of DNA analysis may be limited to patients whose evaluation is indeterminate for a mucinous cyst.

The multicenter pathology-based PANDA study suggested that KRAS followed by LOH mutations could diagnose malignant cysts with 96% specificity and 37% sensitivity[49]. Our group evaluated the diagnostic accuracy for malignant cysts of the 2006 and 2012 IAP guidelines and commercially available DNA analyses (KRAS, LOH mutations, and DNA quantity) in 257 pancreatic cysts[50]. The 2012 guidelines were the most accurate for malignant cysts (90% specificity and 88% sensitivity). The addition of DNA mutation analysis contributed no significant improvement in diagnostic performance. To date, studies of commercial DNA analyses have not been able to clearly define their role in clinical practice[49-53].

Current cyst fluid analyses are unable to consistently differentiate specific cyst types or predict malignant potential[20,54]. Consequently, differentiating benign from pre-malignant cystic lesions remains challenging. Recent studies have found that the preoperative diagnostic accuracy for specific cyst type ranged from 47% to 68% compared to surgical pathology[55,56]; accuracy improved to 73% when cysts were categorized as benign, premalignant and malignant[56]. A retrospective study of 118 patients in a community setting suggested a higher accuracy for EUS (87%) in distinguishing benign, premalignant, and malignant cysts; however, this study is limited because 65% of patients were diagnosed mainly by CT radiologic surveillance with a median follow-up of only 337 d[57].

Therefore, in light of the limitations of current diagnostic tools, novel diagnostic biomarkers have received considerable interest[58]. GNAS mutations have been associated with IPMNs in resected tissue, cyst aspirates and pancreas fluid[59,60]. The combination of GNAS and KRAS mutations in aspirated cyst fluid has been shown to be specific and sensitive for IPMN[61]. Our own study (accepted for publication) on resected cysts found GNAS mutations to be significantly more prevalent in IPMNs (42%) than in SCAs (10%), adenocarcinomas (0%) and MCNs (0%). In addition, double mutations in KRAS and GNAS only occurred in IPMNs (P = 0.006). A recent study of genetic mutations in cyst fluid aspirated by EUS-FNA from 91 cysts found that GNAS mutations occurred in 39% of IPMNs and 22% of IPMNs with adenocarcinoma while KRAS mutations were present in 68% and 78%, respectively[61]. Notably, mutations in either GNAS or KRAS occurred in 83% of IPMNs, 89% of IPMNs with cancer and 6% of MCNs, and no mutations found in PNETs, SCAs and non-neoplastic cysts[61]. The combination of GNAS and KRAS was 98% specific and 84% sensitive for IPMN. Poor sensitivity for MCNs, as in other mutation studies, resulted in only 65% sensitivity for mucinous lesions overall. Neither gene was predictive of malignant potential within mucinous lesions.

MicroRNA (miRNA) are small noncoding RNA which may help diagnose a variety of malignancies and potentially pancreatic cystic lesions as well[62]. We evaluated miRNA in 69 pathology specimens of pancreatic cystic neoplasms, and identified several miRNA panels (4 miRNA in each) that differentiated SCAs from MCNs and IPMNs, and MCNs from BD-IPMNs (sensitivity 85%-100% and specificity 100%)[63]. These promising miRNA panels now need to be validated in EUS-FNA cyst fluid aspirates obtained during diagnostic evaluation. A recent study of the cyst fluid proteome demonstrated that proteomic profiling of mucin in cyst fluid (obtained by EUS-FNA) was 98% accurate for pre-malignant and malignant cysts[64]. A study of select proteins in 22 cyst fluid samples identified a 3 biomarker panel of protein glycoforms that was 91% accurate for mucinous cysts[65]. Metabolomic analysis has demonstrated that metabolites, glucose and kynurenine, were lower in mucinous cysts compared to non-mucinous cysts[66]. These molecular biomarkers may be able to provide improved diagnostic accuracy while requiring only small amounts of fluid, particularly as the number of small cysts identified by imaging continues to increase.

EUS-GUIDED THERAPY

For patients with pancreatic cystic neoplasms that are symptomatic, malignant, or have a high potential for malignant transformation, the current standard of care is surgery. Pancreatic surgical resections are major procedures associated with a high complication

rate (> 40%)[67,68] and long-term morbidity due to loss of pancreatic tissue (*i.e.,* diabetes and exocrine insufficiency). EUS-guided therapies may provide a minimally invasive alternative to surgery in poor or reluctant surgical candidates and a low-risk intervention in cases where conservative management is unsatisfactory because malignant potential is uncertain.

To date ethanol (80%-98%) and paclitaxel have been investigated as ablative agents in pancreatic cysts. Ethanol has effectively destroyed solid and cystic tumors in a number of organs, and elicits better response in pancreatic cysts than saline[69]. Ethanol lavage is believed to induce cell membrane breakdown, rapid protein degradation and vascular blockage[70,71]. Paclitaxel is a commonly used chemotherapeutic agent which stabilizes the microtubule polymer to inhibit its disassembly and consequently induce apoptosis. Its hydrophobic and viscous nature allows it to exert a long-lasting effect on the epithelial lining of the cyst while posing little risk of leakage[72].

Prospective studies evaluating EUS-guided pancreatic cyst ablation have shown cyst resolution (no visible residual cyst on cross-sectional imaging) in 33%-38% of patients using ethanol alone[69,73,74]. Injection of paclitaxel produced improved response with 60%-79% cyst resolution (< 5% of original size on CT follow-up)[75-77]. Long term follow-up of 9 patients who achieved resolution after ethanol lavage found that cyst resolution persisted in all patients over a median 26 mo follow-up (range 13-39 mo)[78]. In 22 patients undergoing EUS-guided ablation with ethanol and paclitaxel, 75% of patients demonstrated at least a 75% reduction in cyst volume (complete cyst resolution in 50% of patients) over a mean 27 mo follow-up (range 17-42 mo), and elimination of pre-operatively detected DNA mutations in LOH and KRAS in 36% of patients[79]. Although this may suggest that ablation leads to DNA changes that decrease risk of malignant progression, this has yet to be proven and new mutations were actually detected in 3 patients.

The technique of EUS-guided pancreatic cyst ablation uses a curvilinear-array echoendoscope. Following cyst puncture with a 22-guage needle, a syringe is used to completely aspirate cyst fluid, similar to when performing standard EUS-FNA of a pancreatic cyst. Complete evacuation of highly viscous fluid may not be possible, and saline injection (0.5-1.0 cc) may help thin the fluid to achieve this[80]. Without removing the needle, the cyst cavity is then injected with ethanol, equal in volume to the aspirated cyst fluid. For 5 min, the cyst cavity is repeatedly evacuated and injected. This involves 3-4 lavages over the 5 min when cyst fluid is thick, or 7-8 lavages if the fluid is thin. The ethanol is then completely removed. If used, paclitaxel is then injected into the cyst but not removed. At no point should the cyst be expanded beyond its original size. Care should be taken to ensure that the needle tip remains within the cyst during the whole procedure to avoid injury to the pancreatic parenchyma and leaks in the cyst wall[80-82].

Ideally, cysts considered amenable to ablation should be benign with no malignant features, 2-4 cm in diameter, uni/oligolocular, and demonstrate no connection with the pancreatic duct. Cysts consistent with MD-IPMN or features suggestive of malignancy should not undergo ablation. Patients with active pancreatitis, ascites, portal hypertension or coagulapathy are also excluded from cyst ablation.

Cyst ablation has been overall well tolerated although complication rates are higher than for EUS-FNA of pancreatic cysts. The most common acute complication is non-specific post-procedure abdominal pain (2%-20%)[69,73-77,79]. Pancreatitis rates range between 2%-10% with no reports of severe pancreatitis, while other less common adverse events include chemical peritonitis with ileus in 3%, gastric wall cyst in 3%, and intracystic bleeding in 2% of cases.

While promising, this procedure is still being studied as concerns about remnant premalignant epithelium, unclear effects on the natural history of cysts, and uncertainty over long term monitoring and outcomes remain[9,78,82].

CONCLUSION

The increasing number of incidentally discovered pancreatic cystic lesions, and their varying potential for malignant transformation, makes accurate diagnosis and choosing appropriate management strategies vitally important. Under current guidelines, EUS and EUS-FNA are critical components in the approach to evaluating and monitoring these lesions. EUS-FNA may provide additional information when the diagnosis is unclear, confirm the presence/absence of features associated with increased risk of malignancy, diagnose malignancy, and monitor for changes in the cysts. Even so, diagnosis remains challenging as current radiologic imaging modalities and EUS-FNA have proven to be limited in diagnostic accuracy. Promising research into new imaging, chemical and molecular biomarkers, as well as EUS-guided therapies may be able to improve diagnosis and management of pancreatic cystic lesions.

REFERENCES

1 **Gardner TB**, Glass LM, Smith KD, Ripple GH, Barth RJ, Klibansky DA, Colacchio TA, Tsapakos MJ, Suriawinata AA, Tsongalis GJ, Pipas JM, Gordon SR. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. *Am J Gastroenterol* 2013; **108**: 1546-1550 [PMID: 24091499 DOI: 10.1038/ajg.2013.103]

2 **Zhang XM**, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology* 2002; **223**: 547-553 [PMID: 11997566 DOI: 10.1148/radiol.2232010815]

3 **Lee KS**, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J*

Gastroenterol 2010; **105**: 2079-2084 [PMID: 20354507 DOI: 10.1038/ajg.2010.122]
4 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]
5 **de Jong K**, Bruno MJ, Fockens P. Epidemiology, diagnosis, and management of cystic lesions of the pancreas. *Gastroenterol Res Pract* 2012; **2012**: 147465 [PMID: 22007199 DOI: 10.1155/2012/147465]
6 **Chung JW**, Chung MJ, Park JY, Bang S, Song SY, Chung JB, Park SW. Clinicopathologic features and outcomes of pancreatic cysts during a 12-year period. *Pancreas* 2013; **42**: 230-238 [PMID: 23146922 DOI: 10.1097/MPA.0b013e31826ae31a]
7 **Klibansky DA**, Reid-Lombardo KM, Gordon SR, Gardner TB. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. *Clin Gastroenterol Hepatol* 2012; **10**: 555-558 [PMID: 22210438 DOI: 10.1016/j.cgh.2011.12.029]
8 **Morris-Stiff G**, Falk GA, Chalikonda S, Walsh RM. Natural history of asymptomatic pancreatic cystic neoplasms. *HPB (Oxford)* 2013; **15**: 175-181 [PMID: 23374357 DOI: 10.1111/j.1477-2574.2012.00522.x]
9 **Farrell JJ**, Fernández-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. *Gastroenterology* 2013; **144**: 1303-1315 [PMID: 23622140 DOI: 10.1053/j.gastro.2013.01.073]
10 **Lee LS**. Incidental Cystic Lesions in the Pancreas: Resect? EUS? Follow? *Curr Treat Options Gastroenterol* 2014; **12**: 333-349 [PMID: 24903582 DOI: 10.1007/s11938-014-0019-6]
11 **Sahani DV**, Kambadakone A, Macari M, Takahashi N, Chari S, Fernandez-del Castillo C. Diagnosis and management of cystic pancreatic lesions. *AJR Am J Roentgenol* 2013; **200**: 343-354 [PMID: 23345356 DOI: 10.2214/AJR.12.8862]
12 **Berland LL**. The American College of Radiology strategy for managing incidental findings on abdominal computed tomography. *Radiol Clin North Am* 2011; **49**: 237-243 [PMID: 21333775 DOI: 10.1016/j.rcl.2010.10.003]
13 **Berland LL**, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, Brink JA, Baker ME, Federle MP, Foley WD, Francis IR, Herts BR, Israel GM, Krinsky G, Platt JF, Shuman WP, Taylor AJ. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. *J Am Coll Radiol* 2010; **7**: 754-773 [PMID: 20889105 DOI: 10.1016/j.jacr.2010.06.013]
14 **Waters JA**, Schmidt CM, Pinchot JW, White PB, Cummings OW, Pitt HA, Sandrasegaran K, Akisik F, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. CT vs MRCP: optimal classification of IPMN type and extent. *J Gastrointest Surg* 2008; **12**: 101-109 [PMID: 17917784 DOI: 10.1007/s11605-007-0367-9]
15 **Macari M**, Finn ME, Bennett GL, Cho KC, Newman E, Hajdu CH, Babb JS. Differentiating pancreatic cystic neoplasms from pancreatic pseudocysts at MR imaging: value of perceived internal debris. *Radiology* 2009; **251**: 77-84 [PMID: 19332847 DOI: 10.1148/radiol.2511081286]
16 **Sainani NI**, Saokar A, Deshpande V, Fernández-del Castillo C, Hahn P, Sahani DV. Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. *AJR Am J Roentgenol* 2009; **193**: 722-731 [PMID: 19696285 DOI: 10.2214/AJR.08.1253]
17 **Kim YC**, Choi JY, Chung YE, Bang S, Kim MJ, Park MS, Kim KW. Comparison of MRI and endoscopic ultrasound in the characterization of pancreatic cystic lesions. *AJR Am J Roentgenol* 2010; **195**: 947-952 [PMID: 20858823 DOI: 10.2214/AJR.09.3985]
18 **Chebib I**, Yaeger K, Mino-Kenudson M, Pitman MB. The role of cytopathology and cyst fluid analysis in the preoperative diagnosis and management of pancreatic cysts > 3 cm. *Cancer Cytopathol* 2014; **122**: 804-809 [PMID: 25044974 DOI: 10.1002/cncy.21460]
19 **Yoon WJ**, Brugge WR. Endoscopic ultrasound and pancreatic cystic lesions-diagnostic and therapeutic applications. *Endosc Ultrasound* 2012; **1**: 75-79 [PMID: 24949341 DOI: 10.7178/eus.02.004]
20 **Al-Haddad M**, Schmidt MC, Sandrasegaran K, Dewitt J. Diagnosis and treatment of cystic pancreatic tumors. *Clin Gastroenterol Hepatol* 2011; **9**: 635-648 [PMID: 21397725 DOI: 10.1016/j.cgh.2011.03.005]
21 **Khalid A**, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol* 2007; **102**: 2339-2349 [PMID: 17764489 DOI: 10.1111/j.1572-0241.2007.01516.x]
22 **Khashab MA**, Kim K, Lennon AM, Shin EJ, Tignor AS, Amateau SK, Singh VK, Wolfgang CL, Hruban RH, Canto MI. Should we do EUS/FNA on patients with pancreatic cysts? The incremental diagnostic yield of EUS over CT/MRI for prediction of cystic neoplasms. *Pancreas* 2013; **42**: 717-721 [PMID: 23558241 DOI: 10.1097/MPA.0b013e3182883a91]
23 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]
24 **Das A**, Ngamruengphong S, Nagendra S, Chak A. Asymptomatic pancreatic cystic neoplasm: a cost-effectiveness analysis of different strategies of management. *Gastrointest Endosc* 2009; **70**: 690-699.e6 [PMID: 19647240 DOI: 10.1016/j.gie.2009.02.013]
25 **Zhong N**, Zhang L, Takahashi N, Shalmiyev V, Canto MI, Clain JE, Deutsch JC, DeWitt J, Eloubeidi MA, Gleeson FC, Levy MJ, Mallery S, Raimondo M, Rajan E, Stevens T, Topazian M. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. *Clin Gastroenterol Hepatol* 2012; **10**: 192-198 [PMID: 21982970 DOI: 10.1016/j.cgh.2011.09.029]
26 **DeWitt J**, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med* 2004; **141**: 753-763 [PMID: 15545675 DOI: 10.7326/0003-4819-141-10-200411160-00006]
27 **Rösch T**, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endosc* 1991; **37**: 347-352 [PMID: 2070987 DOI: 10.1016/S0016-5107(91)70729-3]
28 **Lee KH**, Lee SJ, Lee JK, Ryu JK, Kim EY, Kim TH, Moon JH, Lee WJ, Cho YK, Kim JJ. Prediction of malignancy with endoscopic ultrasonography in patients with branch duct-type intraductal papillary mucinous neoplasm. *Pancreas* 2014; **43**: 1306-1311 [PMID: 25036913 DOI: 10.1097/MPA.0000000000000177]
29 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794 DOI: 10.1053/j.gastro.2004.02.013]
30 **de Jong K**, Verlaan T, Dijkgraaf MG, Poley JW, van Dullemen H, Bruno MJ, Fockens P. Interobserver agreement for endosonography in the diagnosis of pancreatic cysts. *Endoscopy* 2011; **43**: 579-584 [PMID: 21717378 DOI: 10.1055/s-0030-1256434]
31 **Ahmad NA**, Kochman ML, Brensinger C, Brugge WR, Faigel DO, Gress FG, Kimmey MB, Nickl NJ, Savides TJ, Wallace MB, Wiersema MJ, Ginsberg GG. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. *Gastrointest Endosc* 2003; **58**: 59-64 [PMID: 12838222 DOI: 10.1067/mge.2003.298]
32 **Lee LS**, Saltzman JR, Bounds BC, Poneros JM, Brugge WR, Thompson CC. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol* 2005; **3**: 231-236 [PMID: 15765442 DOI: 10.1016/S1542-3565(04)00618-4]
33 **Banerjee S**, Shen B, Baron TH, Nelson DB, Anderson MA, Cash BD, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO,

Jagannath SB, Lichtenstein D, Fanelli RD, Lee K, van Guilder T, Stewart LE. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2008; **67**: 791-798 [PMID: 18374919 DOI: 10.1016/j.gie.2008.02.068]

34 **Layfield LJ**, Ehya H, Filie AC, Hruban RH, Jhala N, Joseph L, Vielh P, Pitman MB. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology. *Diagn Cytopathol* 2014; **42**: 351-362 [PMID: 24639398 DOI: 10.1002/dc.23093]

35 **Maker AV**, Lee LS, Raut CP, Clancy TE, Swanson RS. Cytology from pancreatic cysts has marginal utility in surgical decision-making. *Ann Surg Oncol* 2008; **15**: 3187-3192 [PMID: 18766406 DOI: 10.1245/s10434-008-0110-0]

36 **Attasaranya S**, Pais S, LeBlanc J, McHenry L, Sherman S, DeWitt JM. Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. *JOP* 2007; **8**: 553-563 [PMID: 17873459]

37 **Law JK**, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, Ali SZ, Fishman EK, Kamel I, Canto MI, Dal Molin M, Moran RA, Khashab MA, Ahuja N, Goggins M, Hruban RH, Wolfgang CL, Lennon AM. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? *Pancreas* 2014; **43**: 331-337 [PMID: 24622060 DOI: 10.1097/MPA.0000000000000061]

38 **Jani N**, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, Brugge W, Lee K, Khalid A, McGrath K. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. *Endoscopy* 2008; **40**: 200-203 [PMID: 18067066 DOI: 10.1055/s-2007-995364]

39 **Lee LS**. Diagnosis of pancreatic neuroendocrine tumors and the role of endoscopic ultrasound. *Gastroenterol Hepatol (N Y)* 2010; **6**: 520-522 [PMID: 20978556]

40 **Fonseca R**, Pitman MB. Lymphangioma of the pancreas: a multimodal approach to pre-operative diagnosis. *Cytopathology* 2013; **24**: 172-176 [PMID: 21810124 DOI: 10.1111/j.1365-2303.2011.00897.x]

41 **Morales-Oyarvide V**, Yoon WJ, Ingkakul T, Forcione DG, Casey BW, Brugge WR, Fernández-del Castillo C, Pitman MB. Cystic pancreatic neuroendocrine tumors: the value of cytology in preoperative diagnosis. *Cancer Cytopathol* 2014; **122**: 435-444 [PMID: 24591417 DOI: 10.1002/cncy.21403]

42 **Hong SK**, Loren DE, Rogart JN, Siddiqui AA, Sendecki JA, Bibbo M, Coben RM, Meckes DP, Kowalski TE. Targeted cyst wall puncture and aspiration during EUS-FNA increases the diagnostic yield of premalignant and malignant pancreatic cysts. *Gastrointest Endosc* 2012; **75**: 775-782 [PMID: 22317883 DOI: 10.1016/j.gie.2011.12.015]

43 **Barresi L**, Tarantino I, Traina M, Granata A, Curcio G, Azzopardi N, Baccarini P, Liotta R, Fornelli A, Maimone A, Jovine E, Cennamo V, Fabbri C. Endoscopic ultrasound-guided fine needle aspiration and biopsy using a 22-gauge needle with side fenestration in pancreatic cystic lesions. *Dig Liver Dis* 2014; **46**: 45-50 [PMID: 23916241 DOI: 10.1016/j.dld.2013.06.008]

44 **van der Waaij LA**, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc* 2005; **62**: 383-389 [PMID: 16111956 DOI: 10.1016/S0016-5107(05)01581-6]

45 **Ngamruengphong S**, Bartel MJ, Raimondo M. Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis. *Dig Liver Dis* 2013; **45**: 920-926 [PMID: 23790480 DOI: 10.1016/j.dld.2013.05.002]

46 **Boot C**. A review of pancreatic cyst fluid analysis in the differential diagnosis of pancreatic cyst lesions. *Ann Clin Biochem* 2014; **51**: 151-166 [PMID: 24097809 DOI: 10.1177/0004563213503819]

47 **Nikiforova MN**, Khalid A, Fasanella KE, McGrath KM, Brand RE, Chennat JS, Slivka A, Zeh HJ, Zureikat AH, Krasinskas AM, Ohori NP, Schoedel KE, Navina S, Mantha GS, Pai RK, Singhi AD. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. *Mod Pathol* 2013; **26**: 1478-1487 [PMID: 23743931 DOI: 10.1038/modpathol.2013.91]

48 **Al-Haddad M**, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, Coté G, El Chafic AH, Luz L, Stuart JS, Johnson CS, Klochan C, Imperiale TF. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. *Gastrointest Endosc* 2014; **79**: 79-87 [PMID: 23845445 DOI: 10.1016/j.gie.2013.05.026]

49 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]

50 **Lee LS**, Wu BU, Banks PA, Kadiyala V, Mehta S, Saltzman JR, Thompson CC, Bellizzi AM. Utility of commercial DNA analysis in detecting malignancy within pancreatic cysts. *JOP* 2014; **15**: 182-188 [PMID: 24618422 DOI: 10.6092/1590-8577/2004]

51 **Shen J**, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer* 2009; **117**: 217-227 [PMID: 19415731 DOI: 10.1002/cncy.20027]

52 **Schoedel KE**, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. *Diagn Cytopathol* 2006; **34**: 605-608 [PMID: 16900481 DOI: 10.1002/dc.20511]

53 **Sawhney MS**, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; **69**: 1106-1110 [PMID: 19249035 DOI: 10.1016/j.gie.2008.08.015]

54 **Megibow AJ**, Baker ME, Gore RM, Taylor A. The incidental pancreatic cyst. *Radiol Clin North Am* 2011; **49**: 349-359 [PMID: 21333781 DOI: 10.1016/j.rcl.2010.10.008]

55 **Correa-Gallego C**, Ferrone CR, Thayer SP, Wargo JA, Warshaw AL, Fernández-Del Castillo C. Incidental pancreatic cysts: do we really know what we are watching? *Pancreatology* 2010; **10**: 144-150 [PMID: 20484954 DOI: 10.1159/000243733]

56 **Cho CS**, Russ AJ, Loeffler AG, Rettammel RJ, Oudheusden G, Winslow ER, Weber SM. Preoperative classification of pancreatic cystic neoplasms: the clinical significance of diagnostic inaccuracy. *Ann Surg Oncol* 2013; **20**: 3112-3119 [PMID: 23595223 DOI: 10.1245/s10434-013-2986-6]

57 **Wright GP**, Morrow JB, Shaheen M, Goslin BJ, Baatenburg L, Chung MH. Accuracy of endoscopic ultrasound in the evaluation of cystic pancreatic neoplasms: a community hospital experience. *Pancreas* 2014; **43**: 465-469 [PMID: 24622081 DOI: 10.1097/MPA.0000000000000057]

58 **Lee LS**. Diagnostic approach to pancreatic cysts. *Curr Opin Gastroenterol* 2014; **30**: 511-517 [PMID: 25003604 DOI: 10.1097/MOG.0000000000000098]

59 **Kanda M**, Knight S, Topazian M, Syngal S, Farrell J, Lee J, Kamel I, Lennon AM, Borges M, Young A, Fujiwara S, Seike J, Eshleman J, Hruban RH, Canto MI, Goggins M. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. *Gut* 2013; **62**: 1024-1033 [PMID: 22859495 DOI: 10.1136/gutjnl-2012-302823]

60 **Amato E**, Molin MD, Mafficini A, Yu J, Malleo G, Rusev B, Fassan M, Antonello D, Sadakari Y, Castelli P, Zamboni G, Maitra A, Salvia R, Hruban RH, Bassi C, Capelli P, Lawlor RT, Goggins M, Scarpa A. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. *J Pathol* 2014; **233**: 217-227 [PMID: 24604757 DOI: 10.1002/path.4344]

61 **Singhi AD**, Nikiforova MN, Fasanella KE, McGrath KM, Pai RK, Ohori NP, Bartholow TL, Brand RE, Chennat JS, Lu X, Papachristou GI, Slivka A, Zeh HJ, Zureikat AH, Lee KK, Tsung A, Mantha GS, Khalid A. Preoperative GNAS and KRAS testing in the diagnosis of pancreatic mucinous cysts. *Clin Cancer Res* 2014; **20**: 4381-4389 [PMID: 24938521 DOI: 10.1158/1078-0432.CCR-14-0513]

62 **Lee LS**, Szafranska-Schwarzbach AE, Andruss BF, Conwell DL. Can miRNA biomarkers be utilized to improve the evaluation and management of pancreatic cystic lesions? *MicroRNA*

Diagnostics and Therapeutics 2013; **1**: 24-34 [DOI: 10.2478/micrnat-2013-0003]
63 **Lee LS**, Szafranska-Schwarzbach AE, Wylie D, Doyle LA, Bellizzi AM, Kadiyala V, Suleiman S, Banks PA, Andruss BF, Conwell DL. Investigating MicroRNA Expression Profiles in Pancreatic Cystic Neoplasms. *Clin Transl Gastroenterol* 2014; **5**: e47 [PMID: 24476997 DOI: 10.1038/ctg.2013.18]
64 **Jabbar KS**, Verbeke C, Hyltander AG, Sjövall H, Hansson GC, Sadik R. Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer. *J Natl Cancer Inst* 2014; **106**: djt439 [PMID: 24523528 DOI: 10.1093/jnci/djt439]
65 **Cao Z**, Maupin K, Curnutte B, Fallon B, Feasley CL, Brouhard E, Kwon R, West CM, Cunningham J, Brand R, Castelli P, Crippa S, Feng Z, Allen P, Simeone DM, Haab BB. Specific glycoforms of MUC5AC and endorepellin accurately distinguish mucinous from nonmucinous pancreatic cysts. *Mol Cell Proteomics* 2013; **12**: 2724-2734 [PMID: 23836919 DOI: 10.1074/mcp.M113.030700]
66 **Park WG**, Wu M, Bowen R, Zheng M, Fitch WL, Pai RK, Wodziak D, Visser BC, Poultsides GA, Norton JA, Banerjee S, Chen AM, Friedland S, Scott BA, Pasricha PJ, Lowe AW, Peltz G. Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts: glucose and kynurenine. *Gastrointest Endosc* 2013; **78**: 295-302.e2 [PMID: 23566642 DOI: 10.1016/j.gie.2013.02.037]
67 **Valsangkar NP**, Morales-Oyarvide V, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, Fernández-del Castillo C. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. *Surgery* 2012; **152**: S4-12 [PMID: 22770958 DOI: 10.1016/j.surg.2012.05.033]
68 **Gaujoux S**, Brennan MF, Gonen M, D'Angelica MI, DeMatteo R, Fong Y, Schattner M, DiMaio C, Janakos M, Jarnagin WR, Allen PJ. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. *J Am Coll Surg* 2011; **212**: 590-600; discussion 600-603 [PMID: 21463795 DOI: 10.1016/j.jamcollsurg.2011.01.016]
69 **DeWitt J**, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 2009; **70**: 710-723 [PMID: 19577745 DOI: 10.1016/j.gie.2009.03.1173]
70 **Bean WJ**, Rodan BA. Hepatic cysts: treatment with alcohol. *AJR Am J Roentgenol* 1985; **144**: 237-241 [PMID: 3880981 DOI: 10.2214/ajr.144.2.237]
71 **Gelczer RK**, Charboneau JW, Hussain S, Brown DL. Complications of percutaneous ethanol ablation. *J Ultrasound Med* 1998; **17**: 531-533 [PMID: 9697961]
72 **Rowinsky EK**, Donehower RC. Paclitaxel (taxol) *N Engl J Med* 1995; **332**: 1004-1014 [PMID: 7885406 DOI: 10.1056/NEJM199504133321507]
73 **Gan SI**, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc* 2005; **61**: 746-752 [PMID: 15855986 DOI: 10.1016/S0016-5107(05)00320-2]
74 **DiMaio CJ**, DeWitt JM, Brugge WR. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. *Pancreas* 2011; **40**: 664-668 [PMID: 21562447 DOI: 10.1097/MPA.0b013e3182128d06]
75 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642 [PMID: 18262182 DOI: 10.1016/j.gie.2007.09.038]
76 **Oh HC**, Seo DW, Song TJ, Moon SH, Park do H, Soo Lee S, Lee SK, Kim MH, Kim J. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. *Gastroenterology* 2011; **140**: 172-179 [PMID: 20950614 DOI: 10.1053/j.gastro.2010.10.001]
77 **Oh HC**, Seo DW, Kim SC, Yu E, Kim K, Moon SH, Park do H, Lee SS, Lee SK, Kim MH. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? *Scand J Gastroenterol* 2009; **44**: 242-247 [PMID: 18949629 DOI: 10.1080/00365520802495537]
78 **DeWitt J**, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. *Gastrointest Endosc* 2010; **72**: 862-866 [PMID: 20883866 DOI: 10.1016/j.gie.2010.02.039]
79 **DeWitt JM**, Al-Haddad M, Sherman S, LeBlanc J, Schmidt CM, Sandrasegaran K, Finkelstein SD. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. *Endoscopy* 2014; **46**: 457-464 [PMID: 24770971 DOI: 10.1055/s-0034-1365496]
80 **DeWitt J**. Endoscopic ultrasound-guided pancreatic cyst ablation. *Gastrointest Endosc Clin N Am* 2012; **22**: 291-302, ix-x [PMID: 22632951 DOI: 10.1016/j.giec.2012.04.001]
81 **Oh HC**, Brugge WR. EUS-guided pancreatic cyst ablation: a critical review (with video). *Gastrointest Endosc* 2013; **77**: 526-533 [PMID: 23321339 DOI: 10.1016/j.gie.2012.10.033]
82 **Kelvin YMC**, Park JS, Seo DW. Role of endosonography in the management of incidental pancreatic cystic lesions. *Gastrointest Intervention* 2014; **3**: 40-45 [DOI: 10.1016/j.gii.2014.04.003]

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Advanced endoscopic imaging to improve adenoma detection

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Abstract

Advanced endoscopic imaging is revolutionizing our way on how to diagnose and treat colorectal lesions. Within recent years a variety of modern endoscopic imaging techniques was introduced to improve adenoma detection rates. Those include high-definition imaging, dye-less chromoendoscopy techniques and novel, highly flexible endoscopes, some of them equipped with balloons or multiple lenses in order to improve adenoma detection rates. In this review we will focus on the newest developments in the field of colonoscopic imaging to improve adenoma detection rates. Described techniques include high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy-system.

Key words: Advanced endoscopic imaging; G-Eye; Full Spectrum Endoscopy-system; Chromoendoscopy; I-scan; Narrow band imaging; Fujinon Intelligent Color Enhancement; 3rd Eye; Polyps; Colorectal cancer

Core tip: Here we focus on the newest developments in the field of colonoscopic imaging to improve adenoma detection rates. Described techniques include high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy-system.

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INTRODUCTION

Colorectal cancer is the second most common cause for cancer related death in developed countries. The age-adjusted incidence of colorectal cancer is estimated 61.2 cases and 44.8 cases per 100000

populations among men and women, respectively[1]. Colonoscopy is considered the golden standard for screening of colorectal cancer and its precursor lesions, the colorectal adenomas. The main advantage of colonoscopy in comparison to non-endoscope based screening tests is that it also allows therapy or at least tissue acquisition of colorectal lesions to guide subsequent therapy.

Recently, Nishihara and coworkers examined the association of the use of colonoscopy with colorectal-cancer incidence and colorectal-cancer mortality among participants in the Nurses' Health Study and the Health Professionals Follow-up Study[2]. Overall, more than 88000 participants were followed over a period of 22 years. Within this time, 1815 incident colorectal cancers and 474 deaths from colorectal cancer were documented. Multivariate hazard ratios for colorectal cancer were 0.57 after polypectomy, 0.60 after negative sigmoidoscopy, and 0.44 after negative colonoscopy. In addition, negative colonoscopy was associated with a reduced incidence of proximal colon cancer. Moreover, a reduced mortality from proximal colon cancer was observed after screening colonoscopy but not after sigmoidoscopy. Accordingly, this long-term study confirmed the efficacy of screening colonoscopy to reduce colorectal cancer.

Very recently, Corley and coworkers evaluated the association between the adenoma detection rate and patients' risk of subsequent colorectal cancer (*i.e.,* interval cancer) and death[3]. Over 314000 colonoscopies performed by 136 endoscopists were included. The adenoma detection rates ranged from 7.4% to 52.5%. During the follow-up period, 712 interval cancers were diagnosed. The adenoma detection rate was inversely associated with the risks of interval colorectal cancer, advanced-stage interval cancer, and fatal interval cancer. Importantly, each 1% increase in the adenoma detection rate was associated with a 3% decrease in the risk of colorectal cancer.

Therefore, the above mentioned studies highlighted the importance of a precise colonoscopic examination to reduce colorectal cancer incidence. Within recent years, various new endoscopic imaging techniques have been introduced to assist endoscopists in performing accurate endoscopic examinations. In this review we will focus on the newest developments in the field of colonoscopic imaging including high-definition imaging, optical chromoendoscopy techniques, virtual chromoendoscopy techniques, the Third Eye Retroscope and other retroviewing devices, the G-EYE endoscope and the Full Spectrum Endoscopy (FUSE)-system.

ADVANCED ENDOSCOPIC IMAGING TECHNIQUES

High-definition imaging

Multiple studies have addressed the specific issue whether high-definition white-light imaging is superior to standard white-light endoscopy for diagnosis of colorectal adenomas. Results of those studies are sometimes conflicting. In addition, interpretation is often difficult as new endoscopes are not only equipped with newer chip technology allowing high-definition imaging, but also with wide-field optics and closer focus modes. Therefore, it is not possible to determine which of these individual factors led to altered adenoma detection. One recent meta-analysis compared the diagnostic yield of colonic polyps between high-definition colonoscopy and standard video endoscopy[4]. Five studies involving 4422 patients were included. The incremental yield of high definition colonoscopy for the detection of any polyp was 3.8% with a number needed to treat of 26. For the detection of adenomatous polyps the incremental yield was 3.5% with a number needed to treat of 28. There were no significant differences between high-definition and standard video endoscopy in the detection of high-risk adenomas. Nonetheless, the pooled weighted mean difference in small adenoma detection was significantly higher with high-definition colonoscopy. In a retrospective study including 2430 consecutive patients the adenoma detection rate was significantly higher among patients who underwent high-definition white-light endoscopy compared with standard white-light colonoscopies[5]. These data are in contrast to one recent trial including 426 individuals who underwent high-definition white-light endoscopy and 426 individuals who underwent conventional colonoscopy[6]. In this study, high-definition endoscopy did not increase the detection of individuals with polyps, adenomas, or high-risk adenoma features. High-definition did also not increase the detection of individuals with clinically insignificant colonic lesions.

Importantly, one recent study aimed to investigate whether detection rates of individual endoscopists increase within 1 year before and 1 year after the switch from standard to high-definition endoscopy[7]. In this study, the adenoma detection rates of endoscopists with a low detection rate (< 20%) increased significantly after switch from standard to high-definition endoscopy (P = 0.0076) while this effect was not measurable for high-adenoma detectors ($\geqslant$ 20%).

Optical chromoendoscopy

Optical chromoendoscopy uses optical filters within the light source of the endoscope to narrow the bandwidth of the light. The normal bandwidth consists of a red-green-blue image. The narrow band imaging (NBI; Olympus, Tokyo, Japan) narrows the red light. The resulting green-blue image improves imaging of the mucosal vascular and surface pattern morphology[8].

To date, four meta-analyses evaluated the impact of NBI for colon polyp detection as compared to white-light endoscopy. None of these could find convincing evidence that NBI is significantly better than white-

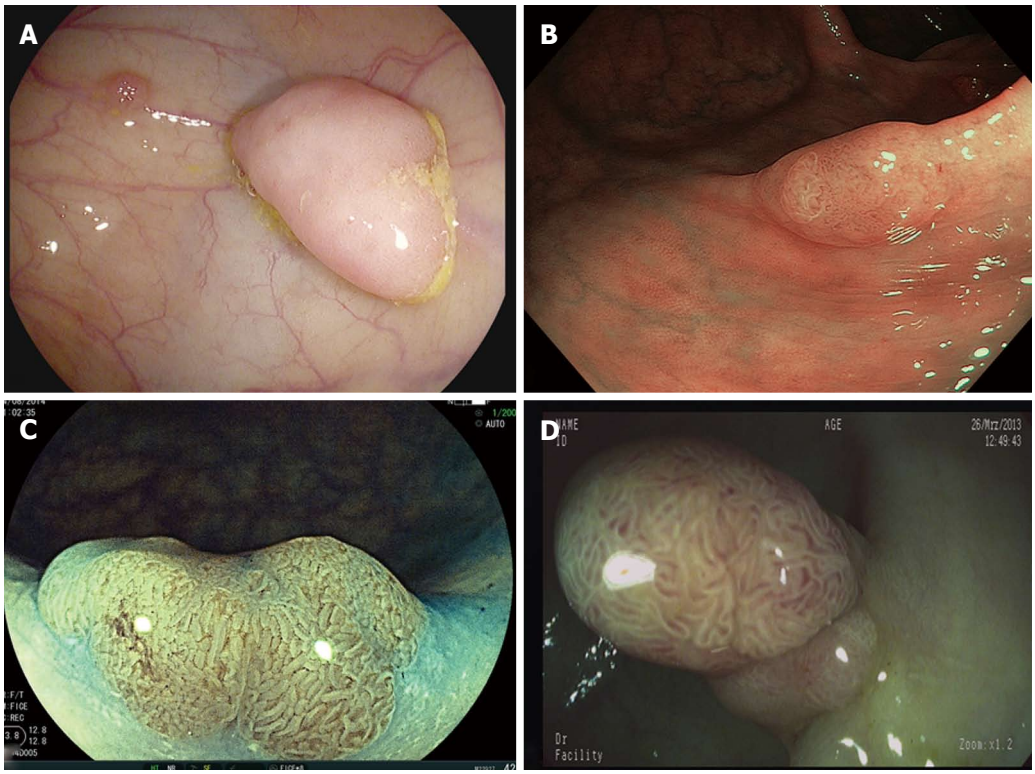

Figure 1 Colonic polyp imaged with high-definition white-light (A), narrow band imaging (B), Fujinon Intelligent Color Enhancement (C) and i-scan (D). Data on detection rates are inconsistent. Nevertheless, dye-less chromoendoscopy techniques allow for a detailed and adequate examination of the mucosal pit pattern and the mucosal vascular pattern morphology to predict polyp histology in real time.

light endoscopy for detection of colorectal polyps[9-12]. The most recent meta-analysis included 7 studies with a total of 2936 patients[12]. No statistically significant difference in the overall polyp or adenoma detection rate with the use of NBI or white-light endoscopy was detected. In addition, when the number of adenomas and polyps per patient was analyzed, no significant difference was found between NBI and white-light endoscopy.

One main disadvantage of the NBI system is the relatively dark image according to its principle of light filtering. While NBI has proven its efficacy for characterization of lesions in multiple studies its value for detection of lesions seems to be limited as the darker NBI image does mostly not allow a detailed view of the colonic structures.

Very recently, a new NBI system was launched (Olympus, Tokyo, Japan), now allowing an up to 4-times brighter image (Figure 1). The new system was already evaluated in a trial by Leung *et al*[13] which included 360 patients. Patients were randomized to undergo either NBI or high-definition white-light endoscopy. In this well designed study, both the adenoma and polyp detection rates were significantly higher in the NBI group as compared with the high-definition white-light group. No significant differences were observed in the adenoma miss rates between the two groups. Therefore, these early results suggest that the new NBI system is superior to conventional white-light endoscopy. The final results of multicenter studies addressing this issue are therefore highly anticipated.

Virtual chromoendoscopy

Virtual chromoendoscopy techniques rely on the principle of digital postprocessing and include Fujinon Intelligent Color Enhancement (FICE, Fujifilm, Tokyo, Japan), i-scan (Pentax, Tokyo, Japan) and the recently introduced SPIES system (Storz, Tuttlingen, Germany) (Figure 2). The technical details of the systems have been reviewed in detail elsewhere[14,15].

Similar to optical chromoendoscopy, results on the efficacy of virtual chromoendoscopy for improved adenoma detection are contrary with studies reporting on improved adenoma detection rates and others not. One early study by Arthur Hoffman included 220 patients which were randomized in a 1:1 ratio to undergo high-definition white-light endoscopy or i-scan[16]. Colonoscopy performed with i-scan detected significantly more patients with colorectal neoplasia (38%) as compared to standard white-light endoscopy (13%). These data were confirmed in a retrospective study by Testoni *et al*[17] reporting significantly more detected lesions with i-scan as compared to standard white-light endoscopy. Contrary, Hong *et al*[18] performed a prospective, randomized trial using a back-to-back colonoscopy design. Overall, 389 patients were randomized. The adenoma detection rates during the first withdrawal of high-definition white-light endoscopy and i-scan and the adenoma miss rates of each group were not statistically different between

Figure 2 RetroView devices allow for a 210 degree bending of the distal tip and are equipped with virtual chromoendoscopy techniques and large working channels to allow adequate characterization of colonic lesions and subsequent endoscopic therapy (Image with kind permission from Fujifilm).

the different groups. Based on the multivariate analysis, the application of i-scan was not associated with an improvement in adenoma detection and the prevention of missed polyps. While there are currently no data on the newly introduced SPIES-system, even the results of studies evaluating the FICE system produced inconsistent data. In this context, one study enrolled 359 patients and randomly assigned those to the white-light group followed by the FICE group and the FICE group followed by the white-light endoscopy group. There was no significant difference between FICE and white-light endoscopy in the adenoma detection rate[19]. Another study examined 135 consecutive patients by total colonoscopy and 128 patients were randomized to compare white-light colonoscopy and FICE[20]. Colonoscopy with FICE identified significantly more patients with small colorectal adenomas than conventional white-light colonoscopy.

Retroscope technology

In 2007, the Third Eye Retroscope (Avantis Medical Systems, Sunnyvale, United Ststes) was introduced[21]. The device consists of a fiber optic which is introduced through the working channel of a standard colonoscope until it extends beyond its other end. Afterwards, the Third Eye Retroscope turns around 180 degrees. The endoscopist has now two images on one monitor. One image is showing the standard colonoscopic view and one image is providing the retrograde view. Main advantage of the system is that it allows to visualize lesions located proximal (*i.e.,* behind) the colonic folds. Various studies have evaluated the Third Eye Retroscope. One multicenter study included eight different centers and a total of 249 patients[22]. 257 polyps were identified with the colonoscope alone while the Third Eye Retroscope detected significantly more additional polyps and adenomas. For lesions 6mm or larger and 10 mm or larger, the additional detection rates with the Third Eye Retroscope for adenomas was 25% and 33%, respectively. Every polyp that was detected with the Third Eye Retroscope was subsequently located with the colonoscope and removed. Another, open-labeled, prospective, multicenter study at nine sites evaluated the impact of the Third Eye Retroscope on adenoma detection rates during colonoscopy[23]. Overall, a 16% increase in the adenoma detection rate by using the Third Eye Retroscope was detected. For lesions 6mm or larger and 10 mm or larger, the overall additional detection rates with the Third Eye Retroscope for all adenomas were 24% and 19%, respectively. Meanwhile, the data have also been confirmed by other investigators demonstrating an improved adenoma detection rate with the Third Eye Retroscope by visualizing areas located proximal (*i.e.,* behind) colonic folds[24,25].

However, despite its efficacy, one potential limitation of the Third Eye Retroscope might be that the working channel is blocked. Accordingly, in order to perform endoscopic therapy of detected lesions, one have to withdraw the device first before advancing additional equipment necessary for polyp removal. In the attempt to offer a hybrid of a therapeutic scope which also allows relatively easy visualization of areas located behind the colonic folds, new "RetroView" devices were recently introduced. These devices (3490TFi, Pentax, Tokyo, Japan and 580RD, Fujifilm, Tokyo, Japan) are slim colonoscopes allowing retroflexion of the distal tip at 210 degrees (Figure 3) In addition, the endoscopes are equipped with latest virtual chromoendoscopy techniques (*i.e.,* i-scan; FICE) and working channels of 3.2mm thereby allowing characterization, demarcation and endoscopic therapy at once. Currently, no scientific evidence regarding the new retroviewing devices is available but multiple groups are already evaluating the potential beneficial effect of the technology.

The FUSE system

FUSE (EndoChoice, GA, United States) was recently introduced as a new platform (Figure 3). The FUSE-colonoscope consists of three imagers integrated into the distal tip of the endoscope and at the lateral sides thereby enabling a 330° angle of view of the colon. Images are displayed on three contiguous monitors. Very recently, Ian Gralnek *et al*[26] presented the results of a large international multicenter study comparing standard forward viewing endoscopy with the FUSE system. Patients underwent same-day, back-to-back tandem colonoscopy with a standard forward-viewing colonoscope and the full-spectrum colonoscope after a 1:1 randomization. Overall, 185 patients were included and randomly assigned to both groups. By per-lesion analysis, the adenoma miss rate was significantly lower in patients receiving FUSE than in those in the standard forward-viewing group (7% *vs* 41%). Therefore, the FUSE platform represents a new and promising technology to improve the efficacy of colorectal cancer screening and surveillance.

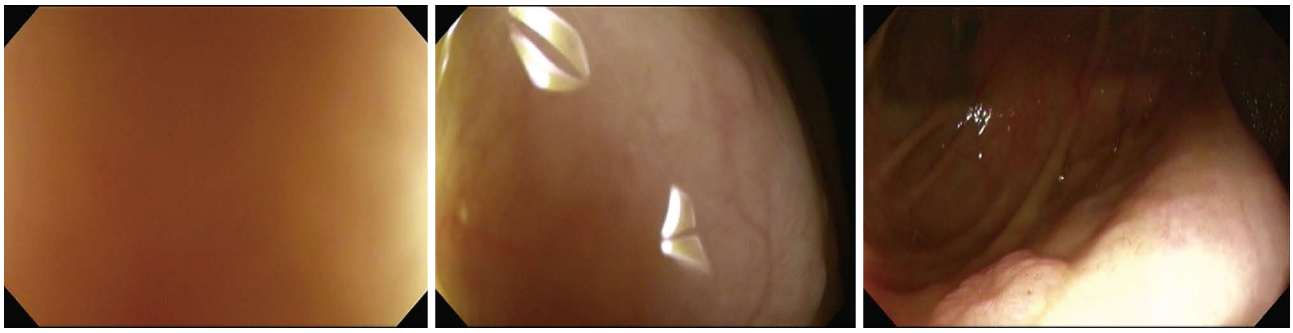

Figure 3 Full Spectrum Endoscopy-System allows 330° imaging on three contiguous monitors. Here, a small non-polypoid lesion located on the proximal part of the ileocecal valve is only visible on the right monitor. Those lesions can easily being missed as they are often located in the realm of the shades.

Figure 4 Newly introduced G-EYE endoscope is equipped with a balloon at the distal bending section of the endoscope. During withdrawal the balloon is inflated thereby stabilizing the endoscope for subsequent therapeutic maneuvers. In addition the balloon yields in a straightening of the colonic folds thereby potentially improving adenoma detection rates (Image with kind permission from Smart Medical).

G-EYE endoscope

Very recently, the G-EYE endoscope (Smart Medical, Ra'anana Israel) was launched. The G-EYE relies on a standard endoscope in which a permanently integrated balloon was incorporated at its distal bending section (Figure 4). The balloon is inflated in the cecum and the endoscope is withdrawn with the balloon inflated until the rectum is reached. The inflated balloon stabilizes the endoscope during the withdrawal phase and interventions and provides additional folds straightening in order to improve adenoma detection rates. Early data provided by Kiesslich and coworkers suggest that the adenoma detection rate with the G-EYE endoscope could be increased by at least 48% (personal communication). Final results of the ongoing multicenter studies are expected by the end of the year.

CONCLUSION

In the attempt to improve adenoma detection rates various advanced endoscopic imaging techniques have been introduced within the past 5 years. Scientific evidence is still missing for some of the new technologies. It is still not fully known whether pure high-definition white-light endoscopy improves adenoma detection rates. Therefore, prospective, randomized, multicenter studies addressing this issue are highly warranted. While there was no beneficial effect of the first NBI system, recent evidence suggests that the new NBI system is superior to conventional white-light endoscopy and could improve adenoma detection rates. Again, results of multicenter studies addressing this issue are highly anticipated. Study results on the potential of virtual chromoendoscopy techniques using digital postprocessing for improved adenoma detection in the colorectum are still inconsistent. Multiple, large and multicenter studies are currently addressing this issue and the results of those studies are anticipated latest within the next two years. New endoscope platforms now allow for a more detailed view of the luminal gastrointestinal tract. Early data demonstrate the impressive potential of those new platforms to improve early diagnosis of colorectal lesions without detriment to procedure time or procedure complications. Therefore, new endoscopic imaging techniques will assist the endoscopists to improve adenoma detection rates for better diagnosis and early therapy of colorectal lesions.

REFERENCES

1 **Lieberman DA**. Clinical practice. Screening for colorectal cancer. *N Engl J Med* 2009; **361**: 1179-1187 [PMID: 19759380 DOI: 10.1056/NEJMcp0902176]

2 **Nishihara R**, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369**: 1095-1105 [PMID: 24047059 DOI: 10.1056/NEJMoa1301969]

3 **Corley DA**, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**: 1298-1306 [PMID: 24693890 DOI: 10.1056/NEJMoa1309086]

4 **Subramanian V**, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**: 499-505 [PMID: 21360420 DOI: 10.1055/s-0030-1256207]

5 **Buchner AM**, Shahid MW, Heckman MG, McNeil RB, Cleveland P, Gill KR, Schore A, Ghabril M, Raimondo M, Gross SA, Wallace MB. High-definition colonoscopy detects colorectal polyps at a higher rate than standard white-light colonoscopy. *Clin Gastroenterol Hepatol* 2010; **8**: 364-370 [PMID: 19932768 DOI: 10.1016/j.cgh.2009.11.009]

6 **Burke CA**, Choure AG, Sanaka MR, Lopez R. A comparison of high-definition versus conventional colonoscopes for polyp detection. *Dig Dis Sci* 2010; **55**: 1716-1720 [PMID: 19707871 DOI: 10.1007/s10620-009-0941-y]

7 **Waldmann E**, Britto-Arias M, Gessl I, Heinze G, Salzl P, Sallinger D, Trauner M, Weiss W, Ferlitsch A, Ferlitsch M. Endoscopists with low adenoma detection rates benefit from high-definition endoscopy. *Surg Endosc* 2015; **29**: 466-473 [PMID: 25005016 DOI: 10.1007/s00464-014-3688-2]

8 **Mönkemüller K**, Fry LC, Zimmermann L, Mania A, Zabielski M, Jovanovic I. Advanced endoscopic imaging methods for colon neoplasia. *Dig Dis* 2010; **28**: 629-640 [PMID: 21088415 DOI: 10.1159/000320065]

9 **Nagorni A**, Bjelakovic G, Petrovic B. Narrow band imaging versus conventional white light colonoscopy for the detection of colorectal polyps. *Cochrane Database Syst Rev* 2012; **1**: CD008361 [PMID: 22258983 DOI: 10.1002/14651858.CD008361.pub2]

10 **Sabbagh LC**, Reveiz L, Aponte D, de Aguiar S. Narrow-band imaging does not improve detection of colorectal polyps when compared to conventional colonoscopy: a randomized controlled trial and meta-analysis of published studies. *BMC Gastroenterol* 2011; **11**: 100 [PMID: 21943365 DOI: 10.1186/1471-230X-11-100]

11 **Pasha SF**, Leighton JA, Das A, Harrison ME, Gurudu SR, Ramirez FC, Fleischer DE, Sharma VK. Comparison of the yield and miss rate of narrow band imaging and white light endoscopy in patients undergoing screening or surveillance colonoscopy: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 363-70; quiz 371 [PMID: 22186978 DOI: 10.1038/ajg.2011.436]

12 **Dinesen L**, Chua TJ, Kaffes AJ. Meta-analysis of narrow-band imaging versus conventional colonoscopy for adenoma detection. *Gastrointest Endosc* 2012; **75**: 604-611 [PMID: 22341105 DOI: 10.1016/j.gie.2011.10.017]

13 **Leung WK**, Lo OS, Liu KS, Tong T, But DY, Lam FY, Hsu AS, Wong SY, Seto WK, Hung IF, Law WL. Detection of colorectal adenoma by narrow band imaging (HQ190) vs. high-definition white light colonoscopy: a randomized controlled trial. *Am J Gastroenterol* 2014; **109**: 855-863 [PMID: 24751581 DOI: 10.1038/ajg.2014.83]

14 **Neumann H**, Fujishiro M, Wilcox CM, Mönkemüller K. Present and future perspectives of virtual chromoendoscopy with i-scan and optical enhancement technology. *Dig Endosc* 2014; **26** Suppl 1: 43-51 [PMID: 24373000 DOI: 10.1111/den.12190]

15 **Tontini GE**, Vecchi M, Neurath MF, Neumann H. Review article: newer optical and digital chromoendoscopy techniques vs. dye-based chromoendoscopy for diagnosis and surveillance in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 1198-1208 [PMID: 24117471 DOI: 10.1111/apt.12508]

16 **Hoffman A**, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S, Galle PR, Neurath MF, Kiesslich R. High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial. *Endoscopy* 2010; **42**: 827-833 [PMID: 20803419 DOI: 10.1055/s-0030-1255713]

17 **Testoni PA**, Notaristefano C, Vailati C, Di Leo M, Viale E. High-definition colonoscopy with i-Scan: better diagnosis for small polyps and flat adenomas. *World J Gastroenterol* 2012; **18**: 5231-5239 [PMID: 23066318 DOI: 10.3748/wjg.v18.i37.5231]

18 **Hong SN**, Choe WH, Lee JH, Kim SI, Kim JH, Lee TY, Kim JH, Lee SY, Cheon YK, Sung IK, Park HS, Shim CS. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. *Gastrointest Endosc* 2012; **75**: 1011-1021.e2 [PMID: 22381530 DOI: 10.1016/j.gie.2011.11.040]

19 **Chung SJ**, Kim D, Song JH, Park MJ, Kim YS, Kim JS, Jung HC, Song IS. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointest Endosc* 2010; **72**: 136-142 [PMID: 20493487 DOI: 10.1016/j.gie.2010.01.055]

20 **Cha JM**, Lee JI, Joo KR, Jung SW, Shin HP. A prospective randomized study on computed virtual chromoendoscopy versus conventional colonoscopy for the detection of small colorectal adenomas. *Dig Dis Sci* 2010; **55**: 2357-2364 [PMID: 19834809 DOI: 10.1007/s10620-009-1003-1]

21 **Triadafilopoulos G**, Watts HD, Higgins J, Van Dam J. A novel retrograde-viewing auxiliary imaging device (Third Eye Retroscope) improves the detection of simulated polyps in anatomic models of the colon. *Gastrointest Endosc* 2007; **65**: 139-144 [PMID: 17185094 DOI: 10.1016/j.gie.2006.07.044]

22 **Waye JD**, Heigh RI, Fleischer DE, Leighton JA, Gurudu S, Aldrich LB, Li J, Ramrakhiani S, Edmundowicz SA, Early DS, Jonnalagadda S, Bresalier RS, Kessler WR, Rex DK. A retrograde-viewing device improves detection of adenomas in the colon: a prospective efficacy evaluation (with videos). *Gastrointest Endosc* 2010; **71**: 551-556 [PMID: 20018280 DOI: 10.1016/j.gie.2009.09.043]

23 **DeMarco DC**, Odstrcil E, Lara LF, Bass D, Herdman C, Kinney T, Gupta K, Wolf L, Dewar T, Deas TM, Mehta MK, Anwer MB, Pellish R, Hamilton JK, Polter D, Reddy KG, Hanan I. Impact of experience with a retrograde-viewing device on adenoma detection rates and withdrawal times during colonoscopy: the Third Eye Retroscope study group. *Gastrointest Endosc* 2010; **71**: 542-550 [PMID: 20189513 DOI: 10.1016/j.gie.2009.12.021]

24 **Leufkens AM**, DeMarco DC, Rastogi A, Akerman PA, Azzouzi K, Rothstein RI, Vleggaar FP, Repici A, Rando G, Okolo PI, Dewit O, Ignjatovic A, Odstrcil E, East J, Deprez PH, Saunders BP, Kalloo AN, Creel B, Singh V, Lennon AM, Siersema PD. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc* 2011; **73**: 480-489 [PMID: 21067735 DOI: 10.1016/j.gie.2010.09.004]

25 **Siersema PD**, Rastogi A, Leufkens AM, Akerman PA, Azzouzi K, Rothstein RI, Vleggaar FP, Repici A, Rando G, Okolo PI, Dewit O, Ignjatovic A, Odstrcil E, East J, Deprez PH, Saunders BP, Kalloo AN, Creel B, Singh V, Lennon AM, DeMarco DC. Retrograde-viewing device improves adenoma detection rate in colonoscopies for surveillance and diagnostic workup. *World J Gastroenterol* 2012; **18**: 3400-3408 [PMID: 22807609 DOI: 10.3748/wjg.v18.i26.3400]

26 **Gralnek IM**, Siersema PD, Halpern Z, Segol O, Melhem A, Suissa A, Santo E, Sloyer A, Fenster J, Moons LM, Dik VK, D'Agostino RB, Rex DK. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. *Lancet Oncol* 2014; **15**: 353-360 [PMID: 24560453 DOI: 10.1016/S1470-2045(14)70020-8]

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MINIREVIEWS

New endoscopic imaging techniques in surveillance of inflammatory bowel disease

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Abstract

Endoscopy plays a crucial role in the management of inflammatory bowel disease (IBD). Advances imaging techniques allow visualization of mucosal details, tissue characteristics and cellular alteration. In particular chromoendoscopy, magnification endoscopy, confocal laser endomicroscopy and endocytoscopy seem to have the possibility to radically modify the approach to surveillance and decision making. Dye-based chromoendoscopy (DBC) and magnification chromoendoscopy improve detection of dysplasia, and evaluation of inflammatory activity and extension of ulcerative colitis and are thus considered the standard of care. Dye-less chromoendoscopy could probably replace conventional DBC for surveillance. Narrow band imaging and i-scan have shown to improve activity and extent assessment in comparison to white-light endoscopy. Confocal laser endomicroscopy (CLE) can detect more dysplastic lesions in surveillance colonoscopy and predict neoplastic and inflammatory changes with high accuracy compared to histology. This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. This combination is useful for appropriate tissue classification of mucosal lesions already detected by standard or optically enhanced endoscopy. The best combination for IBD surveillance appear to be chromoendoscopy for identification of areas of suspicion, with further examination with CLE to detect intraepithelial neoplasia. However cost, availability, and experience are still an issue.

Key words: Ulcerative colitis; Crohn's disease; Endoscopy; Surveillance; Colorectal cancer

Core tip: Modern endoscopic imaging techniques might change the approach to surveillance of patients with inflammatory bowel disease (IBD). They allow visualization of mucosal details, tissue characteristic and cellular changes. In particular chromoendoscopy,

magnification endoscopy, confocal laser endomicroscopy and endocytoscopy promise to radically modify surveillance and decision making in IBD, however their widespread availability and cost/effectiveness is an issue.

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INTRODUCTION

Endoscopy plays a basic role in the diagnosis, management, prognosis and surveillance of inflammatory bowel diseases (IBD). IBD is a chronic lifelong condition that requires careful medical management and follow-up because it can be associated with significant morbidity, need for hospitalization and surgery. Once IBD is suspected based on clinical signs, symptoms, laboratory markers and/or radiology studies, endoscopy with mucosal biopsies is the gold standard to confirm the diagnosis. After diagnosis, endoscopic examination is important to assess the disease extent and severity, to monitor disease activity, to provide endoscopic treatment and for surveillance of dysplasia and neoplasia[1,2]. Patients with longstanding IBD have an increased risk of colorectal cancer (CRC) compared to the general population and the CRC risk appears to be the same in Crohn's colitis and ulcerative colitis (UC)[3,4]. The exact mechanism behind this increased risk are unknown, although data suggest a profound role of chronic inflammation of the intestinal mucosa[5]. There are several meta-analysis evaluating the incidence of CRC in IBD patients. Eaden *et al*[6] reported an overall prevalence of CRC in UC patients of 3.7%, Ekbom found a standardized incidence ratio (SIR) of 5.7 (95%CI: 4.6-7.0)[7] while Bernstein *et al*[8] reported a SIR of 2.3 (95%CI: 2.0-2.6) in UC patients and 2.6 (95%CI: 1.69-4.12) in CD patients. There are many risks factors implicated in the development of CRC: the duration of the inflammatory disease, the extension of the disease, the degree of inflammation, the coexistence of primary sclerosing cholangitis (PSC), and family history of CRC. The association between duration of the disease and development of CRC is the rationale for endoscopic surveillance, that should begin after 7-8 years of initial symptoms complain. The extent of colitis is another important risk factor of CRC risk[9]. CRC risk is high in patients with extensive colitis, intermediate in left-colitis and low in proctitis. Risk assessment of CRC also critically relies on endoscopic appearance of the severity of disease activity: both endoscopic and histological inflammations were shown to be associated with increased risk. The presence of post-inflammatory polyps probably reflects a previous severe inflammation and is associated with an increased risk of CRC development. On these bases, is clear how surveillance endoscopy permits detection of dysplasia and early detection of CRC, leading to an improvement of prognosis[10]. Surveillance should be performed in everyone with UC or Crohn's colitis, except patients with proctitis or Crohn's colitis affecting only one segment of colon. Regarding optimal surveillance intervals there is not clear evidence yet but individualizing intervals based on risk stratification is basic. Patients with an high risk factors for development of CRC should perform a colonscopy every one year (extensive colitis with severe inflammation, diagnosis of PSC, stricture and dysplasia identified in the last five years, history of CRC in a first-degree relative with less than 50 years). Patients with intermediate risk factors should perform a colonscopy every 2-3 years (extensive colitis with mild or moderate inflammation, presence of post-inflammatory polyps, history of CRC in a first degree relative at 50 years and over). For patients with a low risk of CRC, guidelines advise to perform a colonscopy every 5 years[6,7].

CRC mostly develop in raised protruded lesions but it can also occur in flat lesions or in mucosa with normal feature too. In the recent past, raised neoplastic lesions arising within an area of inflammation have been termed dysplasia-associated lesions/masses (DALMs)[11,12]. These lesions may present low or high dysplasia, *in situ* and invasive cancer. Subsequently the term adenoma-like mass (ALM) has been introduced to describe polyps with dysplasia in an area of colitis, but endoscopically very similar to sporadic adenomas[13]. However, no clear endoscopic, histologic or immunohistochemical difference between DALMs, ALMs and sporadic adenomas has been described, although some endoscopic lesions are more common in UC than non-UC patients. Therefore the terms DALM and ALM are more recently dismissed. Actually, lesion's morphology is best described by the standardized terminology of the Paris classification[14] either in abbreviated (0-Ⅱa) or extensive form (*e.g,* flat, minimally elevated lesion), although some irregular or less defined lesions may not be easily categorized. A detailed endoscopic description of morphology, pit pattern, and grade of background mucosal inflammation is requested. Moreover, current terms to describe low and high-grade dysplasia are also low grade non-invasive neoplasia or high grade non-invasive neoplasia, respectively[15]. Surveillance endoscopy white standard light endoscopy and multiple random biopsies may miss a quantum of lesion. Previous literature data showed that in up to 50% of colitis-associated neoplasms, the lesions were not visible at endoscopy[16]. This problem have suggested to perform an high number of random biopsies, every 10 cm of colon in four quadrants, which is a time consuming and costly approach, either for endoscopists and pathologists[17]. Recently,

new emerging endoscopic imaging techniques have been introduced thus allowing a better visualization of mucosal and submucosal lesions[18]. This review will focus on these endoscopic modalities, highlighting their potential role in the surveillance of IBD.

MAGNIFICATION

Magnification endoscopy is performed by an endoscope with a variable lense, which allows to modify the magnification degree until 150-fold. Thanks to this feature is possible to have a detailed characterization of the mucosal surface and the pit pattern. It has been shown that magnification endoscopy combined with chromoendoscopy has the potential to improve targeting biopsy examination in patients with long-standing colitis and facilitate early detection of intraepithelial neoplasia and colorectal cancer[19].

CHROMOENDOSCOPY

Chromoendoscopy uses different staining techniques and endoscopic/optical or computer-based colour programs to enhance the mucosal detail and submucosal vascular pattern; this procedure improve detection of mucosal lesions and permit a more precise characterization. Currently, chromoendoscopy is distinguished in dye-based (DBC) and dye-less imaging techniques (DLC).

Dye agents uses in DBC can be grouped in three types: Contrast agents (Indigo carmine and Acetic acid), Absorptive agents (Toluidine blue, Lugol, Cresyl violet and Methylene blue) and Reactive staining agents (Congo red and Phenol red). These agents are frequently used through spraying or catheters. Chromoendoscopy in combination with high magnification, allows a better definition of spreading and degree of inflammation, if compared with standard white light colonoscopy, in particular in patient with IBD. In addition, these techniques highly improve early detection of intraepithelial CRC[20].

A randomized controlled trial has evaluated the chromoendoscopy for early detection of intraepithelial neoplasia and CRC in UC. A total of 165 patients with long-standing UC were randomized at a 1:1 ratio to undergo conventional colonoscopy or colonoscopy with chromoendoscopy using 0.1% of methylene blue. In the chromoendoscopy group, there was a significantly better correlation between the endoscopic assessment of degree (P = 0.0002) and extent (89% *vs* 52%; P < 0.0001) of colonic inflammation and the histopathologic findings compared, with the conventional colonoscopy group. In addition, significantly more intraepithelial neoplasia were detected in the chromoendoscopy group (32 *vs* 10; P = 0.003). Therefore DBC showed a more accurate diagnosis of extent and grade of inflammatory in UC compared with standard white-light endoscopy and, more importantly, improved early identification of intraepithelial dysplasia and CRC in patients with UC[21]. Some other trials and a meta-analysis evaluated pancolonic chromoendoscopy for detection of dysplasia in UC. Two of these have demonstrated that biopsies guided by dye spray revealed more dysplasia than random biopsies (P = 0.02 and P = 0.001, respectively)[22,23]. A meta-analysis showed a diagnostic odds ratio of 17.5 with a pooled sensitivity of 83.3% and a specificity of 91.3%. Therefore, chromoendoscopy appear to have an high sensitivity with an high diagnostic accuracy for detection of dysplasia[24]. High-magnification chromo-colonoscopy is also a tool for reliable assessment of disease extent in compared to conventional colonoscopy[25]. However, dye-based chromoendoscopy has some potential limitations, mainly its availability but especially the length of procedure. Moreover, dyes do not always coat all surface required and this procedure does not allow a detailed analysis of sub-epithelial capillary network, which is another important feature in the diagnosis of CRC.

DLC is grouped in optical chromoendoscopy and virtual chromoendoscopy. Optical chromoendoscopy include narrow band imaging (NBI; Olympus®). Virtual chromoendoscopy include I-scan (Pentax®) and Fujinon intelligent colour enhancement (FICE; Fujinon®). NBI uses an optical filters, applied on the light source of endoscope, which narrow the bandwidth of spectral transmittance. This methodology highly enhance the visualization of blood vessels pattern. I-scan and FICE, instead, use digital post-processing with computed spectral estimation to achieve a better tissue contrast[26]. The latter are not dependent on the presence of optical filters inside of the video endoscope. FICE and i-scan use endoscopic images and reconstruct virtual images in realtime by increasing the intensity of blue light to a maximum and by decreasing red light and green light to a minimum resulting in an improved contrast of the capillary patterns and enhancement of the mucosal surface. A nice study of Matsumoto *et al*[27] evaluated magnifying colonoscopy with NBI for the diagnosis of intraepithelial neoplasia in ulcerative colitis. In this trial it was showed that the tortuous pattern determined by NBI colonoscopy could be a clue for the diagnosis of dysplasia during surveillance for UC. Van den Broek *et al*[28] undertaken a randomized trial to compare NBI and high definition white-light colonoscopy (HDE). Twenty-five patients with UC underwent NBI or HDE in a random order with at least 3 wk of interval between the two endoscopies. The study showed that NBI does not improve the detection of neoplasia in patients with UC compared to HDE endoscopy. In addition, NBI was insufficient in differentiating neoplastic from non-neoplastic mucosa[28]. Subsequently, Van den Broek *et al*[29], have tested the efficacy of trimodal imaging for the surveillance of

neoplasia in fifty patients with longstanding UC. In the trial, each segment of colon was inspected twice, once with autofluorescence imaging (AFI) and once with standard white light endoscopy, in a randomized order. This study showed that AFI decreased the necessity of random biopsies improving the detection of neoplasia. In addition, NBI pit pattern analysis predicted the histologic findings with a moderate accuracy while AFI colour appeared useful in excluding the presence of neoplasia[29]. In another prospective, randomized study, NBI was compared with CE for the detection of intraepithelial lesions. NBI was less time consuming and equally effective compared to chromoendoscopy for identification of intraepithelial neoplasia (26.9 ± 9.9 min *vs* 15.7 ± 5.6 min, $P < 0.01$). NBI resulted in a significantly lower false-positive biopsy rate and a similar true-positive rate ($P = 0.001$). The percentage of missed intraepithelial neoplasia lesions was superior with NBI, although not reaching statistical significance. However, given the intraepithelial neoplasia miss rate, NBI should not be recommended as the gold standard endoscopic technique for surveillance in IBD[30]. Only one trial tested FICE in a IBD setting, the latter showed that FICE does not improve detection of ulcers and erosions due to Crohn's disease, but this data should be evaluated in larger prospective trials[31]. Finally a study tested the efficacy of high definition (HD) endoscopy compared to i-scan or chromoendoscopy with methylene blue (0.1%) in screening for colorectal cancer and it was found that both i-scan and chromoendoscopy identified more lesions compared to high definition endoscopy alone[12,32].

Given these evidences, ECCO consensus guidelines on endoscopy in IBD recommend pan-colonic methylene blue or indigo carmine chromoendoscopy during surveillance colonoscopy, with targeted biopsies of any visible lesion. When chromoendoscopy is not available multiple random biopsies should be performed.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) has been first introduced in 2004. It can be performed with two devices: one integrated into endoscope (e-CLE; Pentax®, Tokio, Japan), and one using a mini-probe through the scope (p-CLE; Cellvizio, Mauna Kea Technologies, Paris, France). Confocal laser microscopy consists of focusing a laser ray onto the mucosal surface and filtering the returned light by means of a small pinhole which rejects out of focus light. The illumination and detection systems are in the same focal plane and are termed confocal. After passing the pinhole, the fluorescent light is detected by a photo-detection, transforming the light signal into an electrical one, that is recorded by a computer. All detected signals from the illuminated spot are captured and measured. As the laser scans over the plane of interest, a whole image is obtained pixel-by-pixel and line-by-line, whereas the brightness of a resulting image pixel corresponds to the relative intensity of detected fluorescent light. The gray-scale image created is an optical section representing one focal plane within the examined specimen. Real-time confocal laser scanning microscopy-sequences (1 min-duration) are recorded and stored digitally for later evaluation. CLE evaluation and its high-quality images have shown high agreement with the histology[33-35]. A number of studies have investigated the usefulness of CLE in the diagnostic work-up of IBD, especially in ulcerative colitis. CLE has shown that could have a role in assessing the extension and the activity of disease. Moreover it could be useful in targeting biopsies and to improve the early detection of dysplasia. The most recurrent histologic modification in crypt architecture of UC are the crypt dilation, disorganized arrangement of crypts, dilatated spaces between crypts, destruction or fusion of crypts and crypt abscess. The microvascular modifications often consist of dilatation and swelling of branching vessels. Dysplasia is identified by darks cells with depletion of mucin and density reduction of goblet cell. The architectural pattern is often disorganized, epithelial thickness is variable with dark epithelial border and villiform structures. The blood vessels are enlarged with anomalous branching and weak orientation to basement membrane. The Miami classification system has been designed, with a worldwide consensus, for p-CLE images[36]. Due to the technical differences, p-CLE images are not comparable to e-CLE images and there is not a worldwide accepted classification f CLE images in UC, so this is a limitation of this technique[37]. Watanabe *et al*[38] and Li *et al*[39] reported on inflammation activity assessment by CLE. The inflammation activity assessment includes crypt architecture, cellular infiltration, and vessel architecture. These studies showed that images obtained with CLE techniques provided information that are similar to conventional histology, with a good differentiation between active and non-active UC during endoscopy examination. In a double-blind trial, CLE was shown to be superior to NBI[40]. In another study evaluating more than one hundred polyps, probe-based CLE showed a trend of higher sensitivity compared to NBI (86% *vs* 64%, $P = 0.08$), with similar accuracy (82% *vs* 79%, $P = 0.59$). The overall accuracy of using probe-based CLE together with NBI to predict polyp histology was greater than 94%[41]. In the management of patients with UC, an important diagnostic goal, is the detection of dysplasia/neoplasia, with a small number of biopsies, thus minimizing time and cost. In this contest Kiesslich *et al*[42] have shown that identification and diagnosis of dysplasia in UC could be maximized by using together pan-chromoendoscopy and targeted CLE, achieving high value of diagnostic accuracy (sensitivity 94%, specificity 98%). Subsequently this result has been confirmed also by Van den Broek *et al*[43]. A trial of longstanding ulcerative colitis, exploring

the efficacy of the combined application of CE and targeted p-CLE in diagnosing dysplasia, has underlined the high diagnostic accuracy of such procedures compared to standard histology (sensitivity 100%, specificity 90%, positive predictive value 83%, and negative predictive value 100%)[44]. Another recent study prospectively evaluated the clinical applicability and predictive power of endomicroscopy for the *in vivo* differentiation of dysplasia-associated lesional mass (DALM) or adenoma-like mass (ALM). This trial showed that the accuracy of endomicroscopy was 97% with an excellent agreement between endomicroscopy and histopathological diagnosis[45]. Neumann *et al*[46] have explored the clinical utility of CLE also in patients affected by Crohn's disease (CD), determining whether the disease activity can be graded by using CLE. The authors proposed a CLE score for assessing CD activity *in vivo*, with a potential utility of predicting the CD course and response to medical therapy. CLE application in IBD has been evaluated also under a prognostic view. A trial has shown that cell shedding and barrier loss detected by CLE are able to predict relapse of IBD and therefore has a potential role as diagnostic tool for the management. The sensitivity, specificity and accuracy for the CLE grading system to predict a flare were 62.5%, 91.2% and 79%, respectively[47]. A second paper confirmed the prognostic power of CLE in predicting the course for other relevant clinical end-points for patients affected by IBD, such as future hospitalization or surgery[48]. No data are available to compare p-CLE with e-CLE. pCLE has some advantages and disadvantages compared with eCLE. Advantages include the greater versatility of pCLE probes, which can be used in conjunction with virtually any endoscope (high-resolution endoscopes, NBI, cholangioscope, *etc.*), and acquisition at video frame rate of 12 frames/s, allowing *in vivo* imaging of capillary flow. Disadvantages include a slightly lower resolution (approximately1 μm compared with 0.7 μm for eCLE) and smaller field of view (240 μm *vs* 600 μm).This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. So it is useful only for appropriate classification of tissue at a mucosal site already detected by standard or optically enhanced endoscopy. The best combination in IBD surveillance appears to be chromoendoscopy for identification of areas of suspicion, and that examination with CLE to confirm intraepithelial neoplasia. However, confocal techniques are limited by high costs and need of contras media, such as intravenous Fluorescein. In addition, more prolonged time for the procedure is inevitable and the operator's expertise and learning curve is an issue. Larger studies on the combined use of such modalities are required to assess cost/effectiveness.

ENDOCYTOSCOPY

Endocytoscopy (EC; Olympus®) is a new imaging technique, enabling microscopic imaging of the mucosal layer of the gut at a magnification up to 1400-fold. Endocytoscopy is based on a contact light microscope which enables real-time visualization of cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. Systems integrated into the distal tip of an endoscope (iEC) and probe-based (pEC) are available. Probe-based systems consist of handheld miniprobes, inserted through the accessory channel of a standard endoscope. The device provides ultra-high magnification imaging from an optical sampling site of about 0.5 mm in diameter. Endocytoscopy requires preparation of the mucosal layer with absorptive contrast agents like methylene blue or toluidine blue[13]. The technique seems to be useful and safe for the examination of gastrointestinal mucosal surfaces[49], and could recognize neoplasia in aberrant crypt foci and distinguish cancerous lesions from non-cancerous ones[50]. A trial has recently showed the value of EC for assessment of inflammatory disease activity and differentiation of single inflammatory cells in patients with IBD. In that study concordance between EC and histopathology for grading intestinal disease activity in CD was 100%[51].

CONCLUSION

The endoscopy is crucial for diagnosis, prognosis, and management of IBD. In addition, a critical role is that of surveillance of colorectal cancer and detection of dysplasia. In this context the colonoscopy is traditionally coupled with histology, with the need of multiple biopsies. This is suboptimal for dysplasia detection and time consuming for either endoscopists and pathologists. The utilization of chromoendoscopy, possibly combined with magnification, is actually considered the "gold standard", given the adequate diffusion of the methodology and the opportunity to perform targeted rather than random biopsies. In contrast, so far, the techniques of so called virtual or optical chromoendoscopy, although more operator friendly, have not proven to be comparable to chromoendoscopy with vital colorants. However, technology is on progress and several comparative trials underway. Finally, future development and diffusion of confocal endomicroscopy or endocytoscopy could prove further advantage including the need of less biopsies or avoid histology. However, possible medico-legal consequences should be taken into account, and cost/effectiveness, learning curve and length of procedure should be taken into account.

REFERENCES

1 **Annese V**, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kießlich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]

2 **Lashner BA**, Kane SV, Hanauer SB. Colon cancer surveillance

in chronic ulcerative colitis: historical cohort study. *Am J Gastroenterol* 1990; **85**: 1083-1087 [PMID: 2389720]
3 **Choi PM**, Nugent FW, Schoetz DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. *Gastroenterology* 1993; **105**: 418-424 [PMID: 8335197]
4 **Lutgens MW**, Oldenburg B, Siersema PD, van Bodegraven AA, Dijkstra G, Hommes DW, de Jong DJ, Stokkers PC, van der Woude CJ, Vleggaar FP. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. *Br J Cancer* 2009; **101**: 1671-1675 [PMID: 19826420 DOI: 10.1038/sj.bjc.6605359]
5 **Ullman TA**, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology* 2011; **140**: 1807-1816 [PMID: 21530747 DOI: 10.1053/j.gastro.2011.01.057]
6 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535 [PMID: 11247898 DOI: 10.1136/gut.48.4.526]
7 **Ekbom A**, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990; **323**: 1228-1233 [PMID: 2215606 DOI: 10.1056/NEJM199011013231802]
8 **Bernstein CN**, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001; **91**: 854-862 [PMID: 11241255 DOI: 10.1002/1097-0142(20010215)91]
9 **Jess T**, Loftus EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schleck CD, Tremaine WJ, Melton LJ, Munkholm P, Sandborn WJ. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology* 2006; **130**: 1039-1046 [PMID: 16618397 DOI: 10.1053/j.gastro.2005.12.037]
10 **Gupta RB**, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007; **133**: 1099-1105; quiz 1340-1341 [PMID: 17919486 DOI: 10.1053/j.gastro.2007.08.001]
11 **Blackstone MO**, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. *Gastroenterology* 1981; **80**: 366-374 [PMID: 7450425]
12 **Butt JH**, Konishi F, Morson BC, Lennard-Jones JE, Ritchie JK. Macroscopic lesions in dysplasia and carcinoma complicating ulcerative colitis. *Dig Dis Sci* 1983; **28**: 18-26 [PMID: 6822178 DOI: 10.1007/BF01393356]
13 **Bernstein CN**. ALMs versus DALMs in ulcerative colitis: polypectomy or colectomy? *Gastroenterology* 1999; **117**: 1488-1492 [PMID: 10579991 DOI: 10.1016/S0016-5085(99)70300-8]
14 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541]
15 **Schlemper RJ**, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Fléjou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251-255 [PMID: 10896917 DOI: 10.1136/gut.47.2.251]
16 **Bernstein CN**, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994; **343**: 71-74 [PMID: 7903776 DOI: 10.1016/S0140-6736(94)90813-3]
17 **Thomas T**, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25**: 657-668 [PMID: 17311598 DOI: 10.1111/j.1365-2036.2007.03241.x]
18 **Neumann H**, Mönkemüller K, Günther C, Atreya R, Vieth M, Neurath MF. Advanced endoscopic imaging for diagnosis of Crohn's disease. *Gastroenterol Res Pract* 2012; **2012**: 301541 [PMID: 22144998 DOI: 10.1155/2012/301541Epub]
19 **Tontini GE**, Vecchi M, Neurath MF, Neumann H. Advanced endoscopic imaging techniques in Crohn's disease. *J Crohns Colitis* 2014; **8**: 261-269 [PMID: 24080247 DOI: 10.1016/j.crohns.2013.09.004]
20 **Mönkemüller K**, Fry LC, Zimmermann L, Mania A, Zabielski M, Jovanovic I. Advanced endoscopic imaging methods for colon neoplasia. *Dig Dis* 2010; **28**: 629-640 [PMID: 21088415 DOI: 10.1159/000320065]
21 **Kiesslich R**, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003; **124**: 880-888 [PMID: 12671882 DOI: 10.1053/gast.2003.50146]
22 **Marion JF**, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008; **103**: 2342-2349 [PMID: 18844620 DOI: 10.1111/j.1572-0241.2008.01934.x]
23 **Rutter MD**, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004; **53**: 256-260 [PMID: 14724160 DOI: 10.1136/gut.2003.016386]
24 **Wu L**, Li P, Wu J, Cao Y, Gao F. The diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis: meta-analysis of six randomized controlled trials. *Colorectal Dis* 2012; **14**: 416-420 [PMID: 21073646 DOI: 10.1111/j.1463-1318.2010.02505.x]
25 **Hurlstone DP**, Sanders DS, McAlindon ME, Thomson M, Cross SS. High-magnification chromoscopic colonoscopy in ulcerative colitis: a valid tool for in vivo optical biopsy and assessment of disease extent. *Endoscopy* 2006; **38**: 1213-1217 [PMID: 17163321 DOI: 10.1055/s-2006-944732]
26 **Neumann H**, Neurath MF, Mudter J. New endoscopic approaches in IBD. *World J Gastroenterol* 2011; **17**: 63-68 [PMID: 21218085 DOI: 10.3748/wjg.v17.i1.63]
27 **Matsumoto T**, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. *Gastrointest Endosc* 2007; **66**: 957-965 [PMID: 17826773]
28 **van den Broek FJ**, Fockens P, van Eeden S, Stokkers PC, Ponsioen CY, Reitsma JB, Dekker E. Narrow-band imaging versus high-definition endoscopy for the diagnosis of neoplasia in ulcerative colitis. *Endoscopy* 2011; **43**: 108-115 [PMID: 21165822 DOI: 10.1055/s-0030-1255956]
29 **van den Broek FJ**, Fockens P, van Eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. *Gut* 2008; **57**: 1083-1089 [PMID: 18367559 DOI: 10.1136/gut.2007.144097]
30 **Pellisé M**, López-Cerón M, Rodríguez de Miguel C, Jimeno M, Zabalza M, Ricart E, Aceituno M, Fernández-Esparrach G, Ginès A, Sendino O, Cuatrecasas M, Llach J, Panés J. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. *Gastrointest Endosc* 2011; **74**: 840-848 [PMID: 21802681 DOI: 10.1016/j.gie.2011.05.013]
31 **Neumann H**, Fry LC, Bellutti M, Malfertheiner P, Mönkemüller K. Double-balloon enteroscopy-assisted virtual chromoendoscopy for small-bowel disorders: a case series. *Endoscopy* 2009; **41**: 468-471 [PMID: 19418402 DOI: 10.1055/s-0029-1214603]
32 **Hoffman A**, Kagel C, Goetz M, Tresch A, Mudter J, Biesterfeld S, Galle PR, Neurath MF, Kiesslich R. Recognition and characterization of small colonic neoplasia with high-definition colonoscopy using i-Scan is as precise as chromoendoscopy. *Dig Liver Dis* 2010; **42**: 45-50 [PMID: 19473893 DOI: 10.1016/j.dld.2009.04.005]

33 **De Palma GD**, Rispo A. Confocal laser endomicroscopy in inflammatory bowel diseases: dream or reality? *World J Gastroenterol* 2013; **19**: 5593-5597 [PMID: 24039350 DOI: 10.3748/wjg.v19.i34.5593]

34 **Becker V**, Vercauteren T, von Weyhern CH, Prinz C, Schmid RM, Meining A. High-resolution miniprobe-based confocal microscopy in combination with video mosaicing (with video). *Gastrointest Endosc* 2007; **66**: 1001-1007 [PMID: 17767932 DOI: 10.1016/j.gie.2007.04.015]

35 **Kiesslich R**, Goetz M, Neurath MF. Virtual histology. *Best Pract Res Clin Gastroenterol* 2008; **22**: 883-897 [PMID: 18790437 DOI: 10.1016/j.bpg.2008.05.003]

36 **Wallace M**, Lauwers GY, Chen Y, Dekker E, Fockens P, Sharma P, Meining A. Miami classification for probe-based confocal laser endomicroscopy. *Endoscopy* 2011; **43**: 882-891 [PMID: 21818734 DOI: 10.1055/s-0030-1256632]

37 **Salvatori F**, Siciliano S, Maione F, Esposito D, Masone S, Persico M, De Palma GD. Confocal Laser Endomicroscopy in the Study of Colonic Mucosa in IBD Patients: A Review. *Gastroenterol Res Pract* 2012; **2012**: 525098 [PMID: 22474440 DOI: 10.1155/2012/525098]

38 **Watanabe O**, Ando T, Maeda O, Hasegawa M, Ishikawa D, Ishiguro K, Ohmiya N, Niwa Y, Goto H. Confocal endomicroscopy in patients with ulcerative colitis. *J Gastroenterol Hepatol* 2008; **23** Suppl 2: S286-S290 [PMID: 19120913 DOI: 10.1111/j.1440-1746.2008.05559.x]

39 **Li CQ**, Xie XJ, Yu T, Gu XM, Zuo XL, Zhou CJ, Huang WQ, Chen H, Li YQ. Classification of inflammation activity in ulcerative colitis by confocal laser endomicroscopy. *Am J Gastroenterol* 2010; **105**: 1391-1396 [PMID: 19935787 DOI: 10.1038/ajg.2009.664]

40 **Buchner AM**, Shahid MW, Heckman MG, Krishna M, Ghabril M, Hasan M, Crook JE, Gomez V, Raimondo M, Woodward T, Wolfsen HC, Wallace MB. Comparison of probe-based confocal laser endomicroscopy with virtual chromoendoscopy for classification of colon polyps. *Gastroenterology* 2010; **138**: 834-842 [PMID: 19909747 DOI: 10.1053/j.gastro.2009.10.053]

41 **Shahid MW**, Buchner AM, Heckman MG, Krishna M, Raimondo M, Woodward T, Wallace MB. Diagnostic accuracy of probe-based confocal laser endomicroscopy and narrow band imaging for small colorectal polyps: a feasibility study. *Am J Gastroenterol* 2012; **107**: 231-239 [PMID: 22068663 DOI: 10.1038/ajg.2011.376]

42 **Kiesslich R**, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007; **132**: 874-882 [PMID: 17383417 DOI: 10.1053/j.gastro.2007.01.048]

43 **van den Broek FJ**, van Es JA, van Eeden S, Stokkers PC, Ponsioen CY, Reitsma JB, Fockens P, Dekker E. Pilot study of probe-based confocal laser endomicroscopy during colonoscopic surveillance of patients with longstanding ulcerative colitis. *Endoscopy* 2011; **43**: 116-122 [PMID: 21165821 DOI: 10.1055/s-0030-1255954]

44 **Rispo A**, Castiglione F, Staibano S, Esposito D, Maione F, Siano M, Salvatori F, Masone S, Persico M, De Palma GD. Diagnostic accuracy of confocal laser endomicroscopy in diagnosing dysplasia in patients affected by long-standing ulcerative colitis. *World J Gastrointest Endosc* 2012; **4**: 414-420 [PMID: 23125900 DOI: 10.4253/wjge.v4.i9.414]

45 **Hurlstone DP**, Thomson M, Brown S, Tiffin N, Cross SS, Hunter MD. Confocal endomicroscopy in ulcerative colitis: differentiating dysplasia-associated lesional mass and adenoma-like mass. *Clin Gastroenterol Hepatol* 2007; **5**: 1235-1241 [PMID: 17690019 DOI: 10.1016/j.cgh.2007.06.003]

46 **Neumann H**, Vieth M, Atreya R, Grauer M, Siebler J, Bernatik T, Neurath MF, Mudter J. Assessment of Crohn's disease activity by confocal laser endomicroscopy. *Inflamm Bowel Dis* 2012; **18**: 2261-2269 [PMID: 22344873 DOI: 10.1002/ibd.22907]

47 **Kiesslich R**, Duckworth CA, Moussata D, Gloeckner A, Lim LG, Goetz M, Pritchard DM, Galle PR, Neurath MF, Watson AJ. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. *Gut* 2012; **61**: 1146-1153 [PMID: 22115910 DOI: 10.1136/gutjnl-2011-300695]

48 **Turcotte JF**, Wong K, Mah SJ, Dieleman LA, Kao D, Kroeker K, Claggett B, Saltzman JR, Wine E, Fedorak RN, Liu JJ. Increased epithelial gaps in the small intestine are predictive of hospitalization and surgery in patients with inflammatory bowel disease. *Clin Transl Gastroenterol* 2012; **3**: e19 [PMID: 23238291 DOI: 10.1038/ctg.2012.13]

49 **Cipolletta L**, Bianco MA, Rotondano G, Piscopo R, Meucci C, Prisco A, Cipolletta F, de Gregorio A, Salvati A. Endocytoscopy can identify dysplasia in aberrant crypt foci of the colorectum: a prospective in vivo study. *Endoscopy* 2009; **41**: 129-132 [PMID: 19214891 DOI: 10.1055/s-0028-1103452]

50 **Neumann H**, Vieth M, Neurath MF. Image of the month. Endocytoscopy-based detection of focal high-grade intraepithelial neoplasia in colonic polyps. *Clin Gastroenterol Hepatol* 2011; **9**: e13 [PMID: 20851217 DOI: 10.1016/j.cgh.2010.09.004]

51 **Neumann H**, Vieth M, Neurath MF, Atreya R. Endocytoscopy allows accurate in vivo differentiation of mucosal inflammatory cells in IBD: a pilot study. *Inflamm Bowel Dis* 2013; **19**: 356-362 [PMID: 22644957 DOI: 10.1002/ibd.23025]

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Peroral endoscopic myotomy: Time to change our opinion regarding the treatment of achalasia?

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Abstract

Peroral endoscopic myotomy (POEM) is a new endoscopic treatment for achalasia. Compared to the classical surgical myotomy, POEM brings at least the advantage of minimal invasiveness. The data provided until now suggest that POEM offers excellent short-term symptom resolution, with improvement of dysphagia in more than 90% of treated patients, with encouraging manometric outcomes and low incidence of postprocedural gastro-esophageal reflux. The effectiveness of this novel therapy requires long-term follow-up and comparative studies with other treatment modalities for achalasia. This technique requires experts in interventional endoscopy, with a learning curve requiring more than 20 cases, including training on animal and cadaver models, and with a need for structured proctoring during the first cases. This review aims to summarize the data on the technique, outcomes, safety and learning curve of this new endoscopic treatment of achalasia.

Key words: Peroral endoscopic myotomy; Achalasia; Myotomy; Endoscopic treatment

Core tip: This review aims to highlight the importance of a new minimally invasive technique for the treatment of achalasia, compared to classical surgical treatment. Although discovered recently, this method has already imposed itself as a safe and very efficient therapy. The difficult issue in this topic is related to the specialist who performs it and the learning curve in such a rare pathology. The gastroenterologist has to be expert in interventional endoscopy and have special skills in surgery, an excellent knowledge in anatomy and the strength to manage the complications. Considering the low rate of adverse events and the efficacy, as a team already performing POEM, we believe that this is the therapy of the future for achalasia.

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INTRODUCTION

The loss of inhibitory innervation of the lower esophageal sphincter (LES) resulting in inadequate relaxation and higher baseline pressures of the LES defines achalasia. Another feature of achalasia is the absence of esophageal peristalsis, these pathogenic modifications explaining the clinical complaints such as regurgitation, dysphagia, retrosternal pain and weight loss. Achalasia has an incidence of 1/100000 per year, which places this disease in the area of rare pathologies. Otherwise, achalasia is the most frequent primary non malignant disease of the esophagus[1].

Although no treatment with curative intention has been identified, some palliative methods comprising medical, endoscopic and surgical methods have been proposed, all aiming to lower LES pressure. Medical treatment with nitrate and calcium antagonists has proved to have poor efficacy and significant side effects[2-4]. However, some of the medical methods such as smooth muscle relaxants are still used for chest pain relief in patients with vigorous achalasia. Of the endoscopic treatments, Botox injections and pneumatic dilatation (PD) have been traditionally used. Botox injections at the gastroesophageal junction (GEJ) are initially successful in over 90% of patients, but the effects only last for 6-9 mo. Botox injections are therefore generally reserved for elderly patients or poor surgical candidates[5]. Pneumatic dilatation is the nonsurgical technique with the highest success rate[6].

Surgical myotomy was originally reported by Heller in 1913 and consisted of 2 longitudinal incisions of approximately 8 cm on the anterior and posterior esophageal wall, the complete release of the LES being mandatory to achieve complete relief from achalasia symptoms. Later, bilateral myotomy was modified to a single myotomy. One of the limitations and failures of surgical myotomy is gastroesophageal reflux disease (GERD), which was reported in up to 30% of cases, resulting in an additional antireflux procedure, such as fundoplication.

A multicenter study recently published demonstrated no significant differences in clinical success between PD and laparoscopic Heller myotomy (LHM) with fundoplication at a 2 year follow-up[7]. Although these results are no longer available when it comes to a longer follow-up, the failure rate of PD remaining at 50%-60% promotes LHM as the treatment of choice in young patients and in those without special contraindications for surgery[6].

Considering these facts, a new endoscopic technique, the peroral endoscopic myotomy (POEM) that combines the surgical element of a controlled myotomy with the minimal invasiveness of endoscopic approach, imposes itself as a real alternative in the treatment of achalasia[8].

ENDOSCOPIC MYOTOMY

The endoscopy myotomy as a treatment option in achalasia was first described in 1980[9]. A limit of this first report was the use of direct incision of the mucosa, which was considered unsafe and unreliable, so it was abandoned. Later, the technique of endoscopic myotomy through a submucosal channel was described in an animal model[10,11]. Pauli was the first who described the crossing of gastroesophageal junction and esophageal cardiomyotomy[12]. Based on this experimental background, Inoue refined the technique for clinical application in humans, namely POEM[13,14].

During POEM, the muscle layer is intentionally dissected and divided through a submucosal tunnel. Mucosa works as a strong barrier to isolate gastrointestinal lumen from the mediastinum or peritoneum. If the mucosa is kept intact, neither peritonitis nor mediastinitis can occur. Complete endoscopic myotomy was first used in a clinical experience together with the development of the POEM.

POEM PROCEDURE

Indications, contraindications

It is generally recommended that teams beginning a POEM program should do it with approval from an institutional review board and after a learning curve completion. Age under 18, previous esophageal or mediastinal surgery and morbid obesity were previously considered exclusion criteria but are no longer valid today. Fungal infection or heavy esophageal loading with food are also considered contraindications but they can be eventually overcome. A real contraindication for POEM remains the inability to undergo general anesthesia[15] but there are some cases in which POEM has been performed without general anesthesia. POEM is considered to be a safe and effective alternative to the surgical approach in achalasia. The role of POEM in the treatment of other esophageal motor disorders such as diffuse esophageal spasm (DES), non-relaxing hypertensive LES and nutcracker esophagus is still under debate. Also, its role in treating patients with prior conventional therapies for achalasia, in the final stages of achalasia, in children, the elderly and in patients with significant comorbid diseases is still not clear. However, the first reports on this topic are optimistic regarding the benefit of POEM in these pathologies[8,16].

PREOPERATIVE INVESTIGATIONS

On admission to hospital, all patients diagnosed with achalasia complete a standardized validated symptom assessment form, according to the Eckardt classification. Based on the calculated score, the patients are included in different classes of severity. All patients undergo extensive preoperative investigations such as an esophagogastroscopy, barium swallow study and a pH study useful for the diagnosis of an asymptomatic reflux. In the diagnosis and classification

of achalasia, an essential tool is high resolution manometry.

According to the manometric measurements, achalasia is classified into 3 subtypes (Chicago classification)[17]: (1) type Ⅰ (classic achalasia) defined as mean integrated relaxation pressure (IRP) > 15 mmHg and when peristalsis has 100% failed; (2) type Ⅱ (achalasia with compression) as mean IRP > 15 mmHg, abnormal peristalsis, panesophageal pressurization with ≥ 20% of swallows; and (3) type Ⅲ as mean IRP > 15 mmHg, abnormal peristalsis, fragments of distal peristalsis or premature (spastic) contractions with ≥ 20% of swallows preserved.

A group of researchers[18] have elaborated a new endoscopic classification of achalasia based on three structures: multi-ring, crescent-like and diverticulum structure, named Ling classification. They divided achalasia into three types: type Ⅰ, smooth without multi-ring, crescent-like structure or diverticulum structure; type Ⅱ, with multi-ring or crescent-like structure, no diverticulum structure; and type Ⅲ, with diverticulum structure. Type Ⅱ and Ⅲ were also classified into three subtypes (Ⅱa, Ⅱb, Ⅱc; Ⅲ1, Ⅲr and Ⅲ1r). The authors concluded that patients classified as type Ⅰ and Ⅱa patients can be recommended for POEM. Patients included in class Ⅱb are at risk of mucosal damage so they might be considered for POEM, but cautiously. This classification needs further confirmation.

Preoperatively, all patients are recommended to have a liquid diet for at least one day before the procedure and some endoscopists perform an upper endoscopy the day before POEM to wash out the esophagus prior to the intervention. Patients may receive oral antimycotics preoperatively to treat any potential esophageal Candida overgrowth. A prophylactic dose of antibiotics was reported to be given before the procedure. Some authors reported the administration of dexamethasone at the start of the procedure to minimize mucosal edema, which will eventually make the closure of the mucosa more difficult, but this is not clearly stated[19].

TECHNICAL ASPECTS OF POEM

Set up and positioning

The procedure is usually done in the operating room under general anesthesia with endotracheal intubation. The gastroscope used for POEM is a standard one. Some authors use a large working channel endoscope with water jet function, but a slim diagnostic scope can be more suitable sometimes for crossing an extremely narrow GEJ. A transparent distal dissecting small cap or an oblique cap can be used at the tip of the endoscope. In order to avoid mucosal laceration at the mucosal incision site during POEM, an overtube might be placed for stabilization of the scope. Another important device to use during this procedure is the carbon dioxide (CO_2) insufflator, which helps to reduce the risk of complications related to air insufflation (pneumothorax, pneumoperitoneum, embolism and subcutaneous emphysema). The air supply button should expressly be closed during the procedure, even when the CO_2 insufflator is on. A thorough cleaning of the esophageal lumen is done before the beginning of the intervention. Sterile saline should be used during the creation of the submucosal channel given the potential mediastinal or peritoneal entry. Communication with the anesthesia team is essential as the patient may develop tension pneumoperitoneum and may require a decompression of the pneumoperitoneum with a Veress needle[19].

EQUIPMENT REQUIRED FOR POEM

Submucosal tunneling and myotomy are performed commonly using a triangle tip knife (TT knife) with three angulations which spreads the energy towards a wide circumferential range[19]. A high frequency electrosurgical energy generator is required that determines a spray coagulation during tissue dissection in a noncontact manner. It can be effectively used in combination with a special knife, *e.g.,* a TT knife, a hook knife, a water jet or hybrid knife for both submucosal dissection and myotomy[20]. Additionally, for the hemostasis of large bleeding vessels, a monopolar coagulating forceps might be useful during dissection[20].

POEM PROCEDURE

The following technical details of POEM are consistent with those from original reports[2,13,14,19].

General anesthesia

Most frequently, POEM is performed with the patient in a supine position, intubated, under general anesthesia. CO_2 insufflation avoids the risk of air-related complications. CO_2 insufflation does not eliminate the risk of gas entry in the mediastinum or abdomen. It does, however, greatly reduce it because CO_2 is rapidly reabsorbed. The air feeding button will remain closed during POEM. The upper abdomen will be checked from time to time during the whole procedure and if the abdomen is excessively distended, an abdominal wall puncture will be performed in order to prevent abdominal compartment syndrome.

Submucosal tunneling

Mucosal entry: Initially, the distal end of the dissection is marked with methylene blue when performing retroflexion in the stomach. Then, an esophageal mucosal lift is performed with a saline injection containing a small amount of methylene blue or indigo carmine on the right anterior side of the esophageal wall. This is followed by a longitudinal mucosectomy of 1-2 cm. It has to have a longitudinal orientation as transverse incisions are nearly impossible to close. Once the submucosal space is entered, the introduction

of the scope in the submucosa is facilitated by the use of a biliary stone extraction balloon. Then, a dissection fenestrated cap is placed on the tip of the scope for the progression in the submucosal space. A tunnel in the submucosa is created using a combination of spray coagulation, CO_2 insufflation and blunt dissection. The separation of the mucosa from the muscle layer is facilitated by repeated injections of the lifting solution. Researchers have tried to improve the technique of submucosal dissection by using a gel that has the capacity of auto-tunneling[20]. Further studies are needed to confirm the efficacy of this method. The submucosal tunnel should be extended beyond the GEJ for about 2 cm into the proximal stomach.

Identification of GEJ

It is important to correctly identify the GEJ for an adequate myotomy on the gastric side. There are some signs that can be helpful for finding the GEJ: length of insertion of the endoscope, the presence of palisading mucosal vessels, and the transitory increase and later decrease in the resistance of dissection when passing the LES. The increased thickness of the circular muscle bundles of the LES and the yellowish appearance of the submucosal cardial space are an important mark for GEJ. Finally, the discoloration of the cardial mucosa overlying the submucosal tunnel as seen upon retroflexion of the scope in the lumen of the stomach allows the estimation of the distance from the GEJ[19].

Circular muscle myotomy

The circular muscle bundle usually starts to be dissected two centimeters distal to the mucosal entry point in the submucosal tunnel. The progression of the dissection is important as both the mucosa and the longitudinal muscle layer should be preserved. The specialists observed that the standard length of myotomy should be more than 10 cm (12 cm on the esophageal side and 2 cm below the GEJ), with an average of 16 cm, but Inoue reported a myotomy length of up to 25 cm[19]. Given the high incidence of GER post-POEM, there is a tendency to decrease the length of the myotomy, except in cases of vigorous achalasia where a longer myotomy is needed. This tailored approach is facilitated by a new endoluminal imaging probe that measures the GEJ distensibility before and after the selective myotomy[21].

There are some groups of researchers that have compared the full thickness myotomy with a circular muscle myotomy. They concluded that full thickness myotomy improved the procedure time without a significant increase in the procedure-related adverse events or clinical reflux complications. Still, the dissection of the circular muscle layer is generally recommended[22].

Circular muscle dissection advances from proximal to distal and the plane of dissection should be maintained correctly. The confirmation of complete myotomy is immediately provided by the facile passage of the scope through the EGJ at the end of myotomy. When reaching the LES, the dissection of all muscle bundles responsible for achalasia should performed. No anti-reflux procedure is required after the POEM procedure because the external structures of LES are preserved. After completion of the myotomy, the complete relaxation of LES is endoscopically confirmed by the retroflex view of the cardia.

In cases of previous surgical failure, posterior myotomy is recommended to avoid the access to the scar site from the previous surgery.

Closure of mucosal entry

The stomach should be emptied of fluid and gas before closing the mucosa and an antibiotic (*e.g.,* gentamycin) should be spread into the submucosal tunnel[19]. The mucosal entry site, which is usually up to 3 cm long, is closed with endoscopic clips from the distal to proximal end with a distance of a maximum of 3 mm between clips. A few alternative closure methods have been described such as over-the-scope clips (OTSC)[23] and fibrin sealants in the case of perforation of the gastric cardia[24]. Another option described for mucosotomies that cannot be closed is a covered stent[25]. Lately, an endoscopic suturing device with a two layered closure of esophagotomy (OverStitch) has proved to be a good alternative to clips in difficult situations.

Postoperative care

Patients are kept *nil per os* the day after the procedure and they should receive an intravenous proton-pump inhibitor immediately after the end of procedure. The intravenous therapy can be subsequently changed to oral treatment once a *per os* diet is allowed. A gastrografin esophagram should be performed the next day to rule out a mucosal defect and to ensure adequate opening of the GEJ post myotomy. If there is no evidence of radiological complications, the patient can be discharged after 24 h of hospital stay, with recommendations of a liquid diet for one week. There is no consensus for a "second look" EGD within the next days following POEM as it often does not change the management of these patients[16]. As the experience in POEM grows, there are some authors that have reported the release of the patients from hospital on the same day after a normal postoperative contrast esophagography[26].

A 6 mo follow-up is performed after POEM. Patients should undergo follow-up manometry, pH study and esophagogastroscopy. The long-term follow-up consists of performing an upper endoscopy every 5 years in all achalasia patients, given the slightly increased risk for esophageal carcinoma[27].

RESULTS FROM THE DATA PUBLISHED UNTIL NOW-POEM FOR THE TREATMENT OF ACHALASIA

Effectiveness of POEM

The results obtained after treating achalasia can be assessed using clinical data and technical features. The decrease of Eckardt score under 3, the lowering of LES pressure by more than 50% and the improved aspect of barium esophagogram regarding the time of esophageal emptying can define an efficient therapy[28].

The first clinical study performed on a database of 17 patients was published by Inoue *et al*[13]. Blunt dissection combined with electrocautery were used to achieve the dissection of the circular muscle layer. The site of mucosal dissection was closed with endoclips and the procedure was completed in all patients. Regarding complications, pneumoperitoneum occurred in one patient, successfully treated using a needle to puncture the abdominal wall. No case of emphysema was reported postoperatively and no long-term complications occurred. The dysphagia symptom score was significantly reduced (from 10 to 1.3; $P = 0.0003$) and the resting LES pressure decreased from 52.4 to 19.8 ($P = 0.0001$) after POEM.

Since then, new studies have been conducted on the performance of POEM for achalasia, which have confirmed the high success rate of this technique[13,29-44] (Table 1).

The majority of studies published on this theme reported a successful therapy in more than 80% of patients, with significant reductions in the Eckardt score and LES pressure. There were a few studies assessing the efficacy of POEM only with a barium esophagogram, the majority using the decrease of pressure as an objective assessment of treatment. Still, there are new methods promising a high quality evaluation of POEM efficacy, such as EndoFLIP (Endolumenal Functional Lumen Imaging Probe), which provides a quantitative assessment of luminal patency and sphincter distension. EndoFLIP was tested for POEM procedure and surgical myotomy. A similar improvement in EGJ distensibility was demonstrated for both methods. The intraprocedural use of FLIP can be predictive of postoperative symptomatic outcomes, providing evidence that FLIP can be used as a calibration tool during therapeutic procedures for achalasia[45,46].

POEM compared to LHM

As a surgical approach in achalasia, including the relatively new experience with an endoscopic approach, has been used for a number of years, there are already some studies that have compared the efficacy, time of surgery and complications according to these two types of treatment. Teitelbaum *et al*[46] analyzed a group of 17 LHM *vs* a group of 12 POEM patients using timed barium esophagograms before and after the procedure. Both groups had improved column heights after treatment at 1, 2 and 5 min. There was no difference between the procedures in changes from baseline column height. Both operations resulted in a decreased esophageal width and less angulation between the esophageal body and esophagogastric junction. The authors concluded that POEM and LHM have similar anatomical and functional results in the short term. Ujiki *et al*[47] also compared POEM with LHM in 18 *vs* 21 patients and he observed that operative time, myotomy length and complication rates were equal. After treatment, pain differed significantly (POEM 3.9 ± 0.6 *vs* LHM 5.7 ± 0.4, $P = 0.02$ for the visual analog score) and analgesic use was also lower after endoscopic therapy (POEM 26.0 ± 13.7 mg *vs* LHM 90.0 ± 48.5 mg morphine, $P = 0.02$). Return to activities was significantly faster in the POEM group (2.2 ± 0.6 d *vs* 6.4 ± 1.0 d, $P = 0.03$). Postoperative dysphagia and Eckardt scores were not different in the two groups. Different results were reported regarding the pain and analgesia by Hungness *et al*[34]. They observed that pain scores were similar upon post-anesthesia care unit arrival and on postoperative day 1, but were higher at 2 h for POEM patients (3.5 *vs* 2, $P = 0.03$). The operative times were shorter for POEM (113 *vs* 125 min, $P < 0.05$) and estimated blood loss was less (≤ 10 mL in all cases *vs* 50 mL, $P < 0.001$). In terms of efficacy, POEM and LHM appeared to have similar perioperative outcomes. Two other American and European studies reported no differences between the two methods regarding the efficacy and safety[26,48].

POEM for refractory achalasia in the setting of prior interventions

Sharata *et al*[49] analyzed the outcomes of POEM in 12 patients (9 achalasia) in the setting of prior endoscopic interventions. POEM was successfully completed in all patients. The improvement of symptoms was achieved in all patients, based on the Eckardt score from 5 to 1 after POEM. There were no differences regarding perioperative outcomes when compared to POEM performed in patients without previous endoscopic intervention. A case of intramural bleeding was reported and one of dehiscence at the place of mucosotomy. The authors concluded that previous endoscopic therapies do not change the outcomes and complications with POEM. Another study compared 21 patients with failed pneumatic dilation with 30 patients without prior treatment, both groups treated subsequently with POEM. For patients with a failed pneumatic dilation, a significant improvement in the Eckardt score, LES pressure and barium esophagogram was observed after POEM. Regarding the operation time, the patients in the group of previously failed pneumatic dilations had a significantly longer procedure compared to patients without previous treatment of achalasia. The outcomes in terms of efficacy were similar in both groups[50].

Table 1 Efficacy of peroral endoscopic myotomy-data from literature (adapted after[27])

Ref.	*n*	Eckardt score (before/after)	LES pressure (before/after)	Efficacy	Time of follow-up (mo)	Patients with recurrent dysphagia
Inoue *et al*[13]	17	10/1.3	52.4/19	100%	5	0
von Renteln *et al*[30]	16	7.8/0.7	27.2/11.8	94%	3	1
Costamagna *et al*[31]	11	7.1/1.1	45.1/16.9	100%	3	0
Swanstrom *et al*[32]	18	6/0	45/16.8	94%	6	1
Ren *et al*[33]	119	-/<3	29.4/13.5	91.7%	10.4	-
Hungness *et al*[34]	18	7/1	19/9	89%	6	2
Inoue *et al*[35]	300	6.13/1.33	27.3/13.4	98%	12	5
Chiu *et al*[36]	16	5.5/0	43.6/29.8	100%	3	0
Lee *et al*[37]	13	6.4/0.4	30.3/15.3	100%	6.9	0
Minami *et al*[38]	28	6.7/0.7	71.2/21	100%	16	0
Verlaan *et al*[39]	10	8/1	20.5/6.8	-	16	-
Stavropoulos *et al*[40]	66	7.9/0.2	42.5/15.4	96%	13	2
Zhou *et al*[41]	205	Relief in 199/205	-	97%	8.5	3
Von Renteln *et al*[42]	70	6.9/1	27.6/8.9	82%	12	9
Teitelbaum *et al*[43]	41	7/1	22/9	92%	12	-

LES: Lower esophageal sphincter.

When analyzing the surgical Heller myotomy, the persistence of symptoms or the recurrence of them was reported in approximately 10%-20% of patients after 2 years of follow-up[7]. The team conducted by Zhou *et al*[51] published their experience in performing POEM after 11.9 years from primary HLM. The therapeutic efficacy was proved in 11/12 patients with a decrease of the Eckardt score under 3 and a significant improvement of LES pressure. Non-serious complications were reported: one case of mucosal perforation at GEJ managed endoscopically, one case of pneumoperitoneum that needed decompression with needle, and one patient requiring a chest tube for symptomatic pneumothorax.

Although the optimal therapy for these patients is not standardized yet, the authors suggested that POEM is feasible and has excellent results in terms of symptom relief.

Another report of 10 cases was published regarding the use of POEM after surgical myotomy for recurrence of symptoms. A significant decrease in LES pressure after rescue POEM was reported after a follow-up of three months, without complications. They concluded that short-term results of POEM after surgical myotomy were optimistic but long-term results are to be confirmed[52].

A very recent article studying the results of POEM after endoscopic and surgical treatment for achalasia was published. The authors reported excellent results in forty cases of POEM after prior endoscopic or surgical therapies. No differences were found with respect to the short-term outcomes and complications. The authors concluded that POEM is a reliable alternative to surgical techniques but longer follow-up will reveal the real results[53].

ADVERSE EVENTS IN POEM

The rate of serious adverse events of POEM, obtained from the data available until now, is low. The data we are discussing are based on information from the IPOEMS survey[16]. The most frequent complications reported until now are CO_2 retention, capnoperitoneum and mediastinal exposure[27].

Intraoperative adverse events

The risk of aspiration during intubation can be prevented by standard airway protection with a rapid induction time and frequent aspiration of mouth contents. Aspiration as a complication occurs very rarely (< 0.1%)[16]. As we already mentioned in the technique description, the use of CO_2 as the insufflation gas is extremely important. The occurrence of complications related to air or CO_2 insufflation can be prevented if the insufflations are used sparingly when creating the submucosal channel. In less than 10% of cases, a mucosal perforation or bleeding may occur. Regarding inadvertent perforations, as their occurrence is more frequent in full thickness myotomies during POEM, a more robust closure has to be executed[54]. If a lesion of the mucosa occurs during POEM, a tight closure of the breech should be performed using clips in order to prevent the intraluminal content reaching the mediastinum.

Bleeding can occur especially at the distal part of dissection. It is usually controlled with coagulation using the tip of the knife but it is important to have electrosurgical hemostatic forceps for larger bleeding vessels. Some authors reported the use of the endoscope, removed from the submucosal tunnel and advanced in the lumen for compression at the bleeding site.

Regarding the complications related to CO_2 insufflation, physiological effects were reported in some studies. Subcutaneous emphysema may occur in a significant manner in up to 15% of cases, but this is usually well tolerated. Capnothorax is rare (less than 5% of cases) and it is also well tolerated; however, if there are signs of hemodynamic instability, a needle for thoracostomy should be placed to prevent tension

pneumothorax. Capnoperitoneum occurs in up to 50% of the cases but it is clinically insignificant[28].

Postoperative adverse events

Mediastinitis was the most dangerous complication after POEM, due to an esophageal leak. The incidence of mucosal lesions that leads to leakage has been remarkably low (0.2%) and no severe consequences or deaths have been reported. The few cases reported with leaks were drained surgically, without complications[40,52].

Postoperative bleeding also has a low prevalence. The IPOEMS reported a rate of 1% for bleeding[16], with rates of 0.7%[55], 3%[26] and 7%[44] in three prospective series. The management of the bleeding complications was performed conservatively using transfusions as required and clinical observation, but there were some cases that required endoscopic re-intervention with hemostasis or Blakemore tamponade[33,56].

Cardiopulmonary complications are not frequent, although there was one case reported of aspiration pneumonia that required prolonged postoperative recovery[16].

Late adverse events

Incomplete myotomy and GERD are the main sources of treatment failure. The early studies reported a low prevalence of GERD based on symptoms but later studies indicated a higher prevalence of reflux disease, ranging between 20% and 46% after POEM, revealed by endoscopic findings (erosive esophagitis) or abnormal pH study[12-16,18,20-22,24]. The prevalence of GERD after POEM based on pH studies is similar to that reported in large prospective trials after a Heller myotomy with fundoplication[55,57,58].

POEM IN OTHER MOTOR ESOPHAGEAL DISEASES

There are some short reports in small groups of cases with hypertensive motility disorders of esophagus treated with POEM. The efficacy of POEM in patients with diffuse esophageal spasm[39,59-61], hypertensive LES[16,62], type Ⅲ spastic achalasia[1,13,14,16], nutcracker esophagus[38] and jackhammer esophagus[63] has been studied. It has been suggested that pain responds less well to POEM than dysphagia does[16]. An interesting remark is related to a low POEM efficacy in patients with diffuse esophageal spasm and type Ⅲ achalasia but the results observed in hypertensive LES and nutcracker esophagus were optimistic. Longer esophageal myotomy seems to be indicated in diffuse esophageal spasms that are characterized by long spastic segments in the distal esophagus. In the same respect, POEM may be more useful than LHM in motor esophageal disorders as the endoscopic approach allows the proximal extension in the body of the esophagus.

LEARNING CURVE IN PERFORMING POEM

POEM is a treatment for a rare disease, the low prevalence contributing to the difficulty of teaching. The procedure meets the principles of natural orifice transluminal endoscopic surgery (NOTES) and interventional endoscopy. It is a demanding procedure, implying potentially serious adverse effects that should be performed only in specialized centers by experts in interventional endoscopy or surgeons who are skilled in endoscopy. The procedure requires specific knowledge, judgment, technical skills and training, the ability to recognize anatomy and maintain orientation.

The team performing the procedure must be familiar with esophageal pathology, with peculiarities of EGJ, with the technique of submucosal dissection and with the management of the most frequent complications. A learning curve of approximately 20 cases has been proposed to accomplish the training period in POEM for an experienced endoscopist[61]. It has been proved that the length of the procedure and the incidence of inadvertent mucosotomies becomes constant after 20 cases[61].

Training in the laboratory on animal or cadaver models may facilitate the time for the acquisition of skills necessary to perform a POEM. Proctoring at first cases is also necessary. In a meta-analysis published recently, POEM operators pursued preclinical training before a human POEM in 10 of 16 centers analyzed. Most centers used live animal training with fewer centers using *ex vivo* models or cadavers. The extent of preclinical training varied widely (total hours spent on preclinical training ranged from 12 to 154 h). Proctoring was used in 9 of 16 centers in the first cases of a human POEM. The authors mentioned a number of proctored cases ranging between 1 and 7.

There are some studies published focusing on the learning curve of POEM. Kurian *et al*[61] analyzed the learning curve for their first 40 POEMs. The outcomes were assessed using the time of procedure and incidence of perforations. The learning curve seemed to reach a plateau at around 20 procedures. Another study observing the accidental mucosotomies and the number of clips required as a means for acquiring the ability of performing the POEM well demonstrated a learning curve of 7 procedures. The myotomy time was also acquired during these procedures but the tunneling time was not reached during this short practice[64]. Submucosal tunneling seems to be the most challenging part of POEM, with the longest learning curve, but in this study there were not enough patients to analyze the necessary number of procedures for a submucosal tunneling without adverse events.

POEM IN CHILDREN AND THE ELDERLY

A special concern regarding POEM was related to the feasibility of this procedure in patients with

age extremes. Successful therapy was reported in children aged 3 and also in the elderly, the highest age reported being 97. These results encourage us to believe that POEM is a feasible treatment option in different patients irrespective of age, if the patients are selected properly[41,46,65,66].

POEM IN PATIENTS WITH COMORBIDITIES

The majority of experts consider that POEM is not indicated in patients with a history of cirrhosis with portal hypertension, especially in the presence of varices. Severe coagulopathy could be a contraindication as well as prior interventions resulting in significant submucosal fibrosis, such as esophageal irradiation and ablation therapy. Pulmonary fibrosis with respiratory failure makes POEM difficult to recommend in patients with this type of pathology[16].

CONCLUSION

POEM appears to be a feasible endoscopic therapy for achalasia with excellent short-term clinical results and improvement in manometric outcomes. Compared to the classical gold standard approach (surgical myotomy), it is a minimally invasive procedure with good outcomes and a safe profile. On the other hand, POEM is a sophisticated and technically demanding procedure that should be performed only by experts in interventional endoscopy and developed in equipped technical centers with numerous cases of achalasia. Further prospective randomized trials are required to compare the effectiveness of POEM with other actual therapies and to establish its long-term outcomes for the management of achalasia.

REFERENCES

1 **Gockel HR**, Schumacher J, Gockel I, Lang H, Haaf T, Nöthen MM. Achalasia: will genetic studies provide insights? *Hum Genet* 2010; **128**: 353-364 [PMID: 20700745 DOI: 10.3238/arztebl.2012.0209]

2 **Eleftheriadis N**, Inoue H, Ikeda H, Onimaru M, Yoshida A, Hosoya T, Maselli R, Kudo SE. Training in peroral endoscopic myotomy (POEM) for esophageal achalasia. *Ther Clin Risk Manag* 2012; **8**: 329-342 [PMID: 22888256 DOI: 10.2147/TCRM.S32666]

3 **Beck WC**, Sharp KW. Achalasia. *Surg Clin North Am* 2011; **91**: 1031-1037 [PMID: 21889028 DOI: 10.1016/j.suc.2011.06.005]

4 **Vaezi MF**, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013; **108**: 1238-1249; quiz 1250 [PMID: 23877351 DOI: 10.1038/ajg.2013.196]

5 **Chuah SK**, Hsu PI, Wu KL, Wu DC, Tai WC, Changchien CS. 2011 update on esophageal achalasia. *World J Gastroenterol* 2012; **18**: 1573-1578 [PMID: 22529685 DOI: 10.3748/wjg.v18.i14.1573]

6 **Allaix ME**, Patti MG. What is the best primary therapy for achalasia: medical or surgical treatment? Who owns achalasia? *J Gastrointest Surg* 2013; **17**: 1547-1549 [PMID: 23780637 DOI: 10.1007/s11605-013-2252-z]

7 **Boeckxstaens GE**, Annese V, des Varannes SB, Chaussade S, Costantini M, Cuttitta A, Elizalde JI, Fumagalli U, Gaudric M, Rohof WO, Smout AJ, Tack J, Zwinderman AH, Zaninotto G, Busch OR. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; **364**: 1807-1816 [PMID: 21561346 DOI: 10.1056/NEJMoa1010502]

8 **Swanstrom LL**. Peroral endoscopic myotomy for treatment of achalasia. *Gastroenterol Hepatol (N Y)* 2012; **8**: 613-615 [PMID: 23483860]

9 **Ortega JA**, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; **26**: 8-10 [PMID: 7358270 DOI: 10.1016/j.gie.2010.04.016]

10 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382 DOI: 10.1055/s-2007-966764]

11 **Sumiyama K**, Gostout CJ, Rajan E, Bakken TA, Knipschield MA, Marler RJ. Submucosal endoscopy with mucosal flap safety valve. *Gastrointest Endosc* 2007; **65**: 688-694 [PMID: 17324411 DOI: 10.1016/j.gie.2006.07.030]

12 **Pauli EM**, Mathew A, Haluck RS, Ionescu AM, Moyer MT, Shope TR, Rogers AM. Technique for transesophageal endoscopic cardiomyotomy (Heller myotomy): video presentation at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2008, Philadelphia, PA. *Surg Endosc* 2008; **22**: 2279-2280 [PMID: 18622556 DOI: 10.1007/s00464-008-0035-5]

13 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]

14 **Inoue H**, Minami H, Satodate H, Kudo S. First clinical experience of submucosal endoscopic myotomy for esophageal achalasia with no skin incision. *Gastrointest Endosc* 2009; **69**: AB122 [DOI: 10.1016/j.gie.2009.03.133]

15 **Swanstrom LL**, Kurian A, Dunst CM, Sharata A, Bhayani N, Rieder E. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. *Ann Surg* 2012; **256**: 659-667 [PMID: 22982946 DOI: 10.1097/SLA.0b013e31826b5212]

16 **Stavropoulos SN**, Modayil RJ, Friedel D, Savides T. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. *Surg Endosc* 2013; **27**: 3322-3338 [PMID: 23549760 DOI: 10.1007/s00464-013-2913-8]

17 **Pandolfino JE**, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008; **135**: 1526-1533 [PMID: 18722376 DOI: 10.1053/j.gastro.2008.07.022]

18 **Li HK**, Linghu EQ. New endoscopic classification of achalasia for selection of candidates for peroral endoscopic myotomy. *World J Gastroenterol* 2013; **19**: 556-560 [PMID: 23382636 DOI: 10.3748/wjg.v19.i4.556]

19 **Inoue H**, Santi EG, Onimaru M, Kudo SE. Submucosal endoscopy: from ESD to POEM and beyond. *Gastrointest Endosc Clin N Am* 2014; **24**: 257-264 [PMID: 24679236 DOI: 10.1016/j.giec.2013.12.003]

20 **Khashab MA**, Sharaiha RZ, Saxena P, Law JK, Singh VK, Lennon AM, Shin EJ, Canto MI, Aguila G, Okolo PI, Stavropoulos SN, Inoue H, Pasricha PJ, Kalloo AN. Novel technique of auto-tunneling during peroral endoscopic myotomy (with video). *Gastrointest Endosc* 2013; **77**: 119-122 [PMID: 23261101 DOI: 10.1016/j.gie.2012.09.011]

21 **Rieder E**, Swanström LL, Perretta S, Lenglinger J, Riegler M, Dunst CM. Intraoperative assessment of esophagogastric junction distensibility during per oral endoscopic myotomy (POEM) for esophageal motility disorders. *Surg Endosc* 2013; **27**: 400-405 [PMID: 22955896 DOI: 10.1007/s00464-012-2484-0]

22 **Li QL**, Chen WF, Zhou PH, Yao LQ, Xu MD, Hu JW, Cai MY, Zhang YQ, Qin WZ, Ren Z. Peroral endoscopic myotomy for the treatment of achalasia: a clinical comparative study of endoscopic full-thickness and circular muscle myotomy. *J Am Coll Surg* 2013; **217**: 442-451 [PMID: 23891074 DOI: 10.1016/j.jamcollsurg.2013.

04.033]
23 **Saxena P**, Chavez YH, Kord Valeshabad A, Kalloo AN, Khashab MA. An alternative method for mucosal flap closure during peroral endoscopic myotomy using an over-the-scope clipping device. *Endoscopy* 2013; **45**: 579-581 [PMID: 23592391 DOI: 10.1055/s-0032-1326398]
24 **Li H**, Linghu E, Wang X. Fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy (POEM). *Endoscopy* 2012; **44** Suppl 2 UCTN: E215-E216 [PMID: 22622752 DOI: 10.1055/s-0032-1309358]
25 **Ling T**, Pei Q, Pan J, Zhang X, Lv Y, Li W, Zou X. Successful use of a covered, retrievable stent to seal a ruptured mucosal flap safety valve during peroral endoscopic myotomy in a child with achalasia. *Endoscopy* 2013; **45** Suppl 2 UCTN: E63-E64 [PMID: 23526520 DOI: 10.1055/s-0032-1325977]
26 **Bhayani NH**, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. *Ann Surg* 2014; **259**: 1098-1103 [PMID: 24169175 DOI: 10.1097/SLA.0000000000000268]
27 **Rohof WO**, Boeckxstaens GE. Treatment of the patient with achalasia. *Curr Opin Gastroenterol* 2012; **28**: 389-394 [PMID: 22508324 DOI: 10.1097/MOG.0b013e328353af8f]
28 **Stavropoulos SN**, Desilets DJ, Fuchs KH, Gostout CJ, Haber G, Inoue H, Kochman ML, Modayil R, Savides T, Scott DJ, Swanstrom LL, Vassiliou MC. Per-oral endoscopic myotomy white paper summary. *Gastrointest Endosc* 2014; **80**: 1-15 [PMID: 24950639 DOI: 10.1016/j.gie.2014.04.014]
29 **Inoue H**, Tianle KM, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Minami H, Kudo SE. Peroral endoscopic myotomy for esophageal achalasia: technique, indication, and outcomes. *Thorac Surg Clin* 2011; **21**: 519-525 [PMID: 22040634 DOI: 10.1016/j.thorsurg.2011.08.005]
30 **von Renteln D**, Inoue H, Minami H, Werner YB, Pace A, Kersten JF, Much CC, Schachschal G, Mann O, Keller J, Fuchs KH, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012; **107**: 411-417 [PMID: 22068665 DOI: 10.1038/ajg.2011.388]
31 **Costamagna G**, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012; **44**: 827-832 [PMID: 22609465 DOI: 10.1016/j.dld.2012.04.003]
32 **Swanström LL**, Rieder E, Dunst CM. A stepwise approach and early clinical experience in peroral endoscopic myotomy for the treatment of achalasia and esophageal motility disorders. *J Am Coll Surg* 2011; **213**: 751-756 [PMID: 21996484 DOI: 10.1016/j.jamcollsurg.2011.09.001]
33 **Ren Z**, Zhong Y, Zhou P, Xu M, Cai M, Li L, Shi Q, Yao L. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc* 2012; **26**: 3267-3272 [PMID: 22609984 DOI: 10.1007/s00464-012-2336-y]
34 **Hungness ES**, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, Soper NJ. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *J Gastrointest Surg* 2013; **17**: 228-235 [PMID: 23054897 DOI: 10.1007/s11605-012-2030-3]
35 **Inoue H**, Ikeda H, Onimaru M, Yoshida A, Sato H, Santi E, Maselli R, Eleftheriadis N, Kudo S. Clinical results in 300 cases of POEM for esophageal achalasia a single institute registered prospective study [abstract]. *Gastrointest Endosc* 2013; **77** Suppl 5: AB121-AB122 [DOI: 10.1016/j.gie.2013.04.007]
36 **Chiu PW**, Wu JC, Teoh AY, Chan Y, Wong SK, Liu SY, Yung MY, Lam CC, Sung JJ, Chan FK, Lau JY, Ng EK. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013; **77**: 29-38 [PMID: 23043852 DOI: 10.1016/j.gie.2012.08.018]
37 **Lee BH**, Shim KY, Hong SJ, Bok GH, Cho JH, Lee TH, Cho JY. Peroral endoscopic myotomy for treatment of achalasia: initial results of a korean study. *Clin Endosc* 2013; **46**: 161-167 [PMID: 23614126 DOI: 10.5946/ce.2013.46.2.161]
38 **Minami H**, Isomoto H, Yamaguchi N, Matsushima K, Akazawa Y, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc* 2014; **26**: 43-51 [PMID: 23581563 DOI: 10.1111/den.12086]
39 **Verlaan T**, Rohof WO, Bredenoord AJ, Eberl S, Rösch T, Fockens P. Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointest Endosc* 2013; **78**: 39-44 [PMID: 23453184 DOI: 10.1016/j.gie.2013.01.006]
40 **Stavropoulos SN**, Modayil RJ, Brathwaite CE. POEM (per oral endoscopic myotomy) for achalasia: excellent long-term safety and efficacy and durability in a large single center 4 year series. *Am J Gastroenterol* 2013; **108** Suppl 1: S619
41 **Zhou P**, Yao L, Zhang YQ, Cai MY, Zhong YS, Ren Z, Xu MD, Chen WF, Li QL, Qin XY. Peroral endoscopic myotomy (POEM) for esophageal achalasia: 205 cases report. *Gastrointest Endosc* 2012; **75**: AB132-AB133 [DOI: 10.1016/j.gie.2012.04.042]
42 **Von Renteln D**, Fuchs KH, Fockens P, Bauerfeind P, Vassiliou MC, Werner YB, Fried G, Breithaupt W, Heinrich H, Bredenoord AJ, Kersten JF, Verlaan T, Trevisonno M, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology* 2013; **145**: 309-11.e1-3 [PMID: 23665071 DOI: 10.1053/j.gastro.2013.04.057]
43 **Teitelbaum EN**, Soper NJ, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, Hirano I, Hungness ES. Symptomatic and physiologic outcomes one year after peroral esophageal myotomy (POEM) for treatment of achalasia. *Surg Endosc* 2014; **28**: 3359-3365 [PMID: 24939164 DOI: 10.1007/s00464-014-3628-1]
44 **Teitelbaum EN**, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, Nicodème F, Lin Z, Hungness ES. Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surg Endosc* 2015; **29**: 522-528 [PMID: 25055891]
45 **Teitelbaum EN**, Boris L, Arafat FO, Nicodème F, Lin Z, Kahrilas PJ, Pandolfino JE, Soper NJ, Hungness ES. Comparison of esophagogastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. *Surg Endosc* 2013; **27**: 4547-4555 [PMID: 24043641 DOI: 10.1007/s00464-013-3121-2]
46 **Teitelbaum EN**, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, Hungness ES. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery* 2013; **154**: 885-891; discussion 891-892 [PMID: 24074428 DOI: 10.1016/j.surg.2013.04.051]
47 **Ujiki MB**, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery* 2013; **154**: 893-897; discussion 893-897 [PMID: 24074429 DOI: 10.1016/j.surg.2013.04.042]
48 **Von Renteln D**, Fuchs KH, Fockens P, Bauerfeind P, Vassiliou MC, Werner YB, Gockel I, Fried GM, Breithaupt W, Heinrich H, Bredenoord AJ, Kersten JF, Verlaan T, Trevisonno M, RöSch T. Endoscopic versus surgical myotomy for idiopathic achalasia: results of a prospective multicenter study and comparison with laparoscopic surgery. *Gastrointest Endosc* 2013; **77** Suppl 5: AB122 [DOI: 10.1016/j.gie.2013.04.008]
49 **Sharata A**, Kurian AA, Dunst CM, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013; **17**: 1188-1192 [PMID: 23609138 DOI: 10.1007/s11605-013-2193-6]
50 **Ling T**, Guo H, Zou X. Effect of peroral endoscopic myotomy in achalasia patients with failure of prior pneumatic dilation: a prospective case-control study. *J Gastroenterol Hepatol* 2014; **29**: 1609-1613 [PMID: 24628480 DOI: 10.1111/jgh.12570]
51 **Zhou PH**, Li QL, Yao LQ, Xu MD, Chen WF, Cai MY, Hu JW, Li L, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Cui Z. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. *Endoscopy* 2013; **45**: 161-166 [PMID: 23389963 DOI:

10.1055/s-0032-1326203]
52 **Onimaru M**, Inoue H, Ikeda H, Yoshida A, Santi EG, Sato H, Ito H, Maselli R, Kudo SE. Peroral endoscopic myotomy is a viable option for failed surgical esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. *J Am Coll Surg* 2013; **217**: 598-605 [PMID: 23891071 DOI: 10.1016/j.jamcollsurg.2013.05.025]
53 **Kurian AA**, Bhayani NH, Reavis K, Dunst C, Swanström L. Endoscopic suture repair of full-thickness esophagotomy during per-oral esophageal myotomy for achalasia. *Surg Endosc* 2013; **27**: 3910 [PMID: 23708719 DOI: 10.1007/s00464-013-3002-8]
54 **Orenstein SB**, Raigani S, Wu YV, Pauli EM, Phillips MS, Ponsky JL, Marks JM. Peroral endoscopic myotomy (POEM) leads to similar results in patients with and without prior endoscopic or surgical therapy. *Surg Endosc* 2014; Epub ahead of print [PMID: 25249143]
55 **Cai MY**, Zhou PH, Yao LQ, Xu MD, Zhong YS, Li QL, Chen WF, Hu JW, Cui Z, Zhu BQ. Peroral endoscopic myotomy for idiopathic achalasia: randomized comparison of water-jet assisted versus conventional dissection technique. *Surg Endosc* 2014; **28**: 1158-1165 [PMID: 24232052 DOI: 10.1007/s00464-013-3300-1]
56 **Li QL**, Zhou PH, Yao LQ, Xu MD, Chen WF, Hu JW, Cai MY, Zhang YQ, Zhong YS, Qin WZ, He MJ. Early diagnosis and management of delayed bleeding in the submucosal tunnel after peroral endoscopic myotomy for achalasia (with video). *Gastrointest Endosc* 2013; **78**: 370-374 [PMID: 23680177 DOI: 10.1016/j.gie.2013.04.172]
57 **Khajanchee YS**, Kanneganti S, Leatherwood AE, Hansen PD, Swanström LL. Laparoscopic Heller myotomy with Toupet fundoplication: outcomes predictors in 121 consecutive patients. *Arch Surg* 2005; **140**: 827-833; discussion 833-834 [PMID: 16172290 DOI: 10.1001/archsurg.140.9.827]
58 **Rawlings A**, Soper NJ, Oelschlager B, Swanstrom L, Matthews BD, Pellegrini C, Pierce RA, Pryor A, Martin V, Frisella MM, Cassera M, Brunt LM. Laparoscopic Dor versus Toupet fundoplication following Heller myotomy for achalasia: results of a multicenter, prospective, randomized-controlled trial. *Surg Endosc* 2012; **26**: 18-26 [PMID: 21789646 DOI: 10.1007/s00464-011-1822-y]
59 **Shiwaku H**, Inoue H, Beppu R, Nakashima R, Minami H, Shiroshita T, Yamauchi Y, Hoshino S, Yamashita Y. Successful treatment of diffuse esophageal spasm by peroral endoscopic myotomy. *Gastrointest Endosc* 2013; **77**: 149-150 [PMID: 22482919 DOI: 10.1016/j.gie.2012.02.008]
60 **Louis H**, Covas A, Coppens E, Devière J. Distal esophageal spasm treated by peroral endoscopic myotomy. *Am J Gastroenterol* 2012; **107**: 1926-1927 [PMID: 23211862 DOI: 10.1038/ajg.2012.317]
61 **Kurian AA**, Dunst CM, Sharata A, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic esophageal myotomy: defining the learning curve. *Gastrointest Endosc* 2013; **77**: 719-725 [PMID: 23394838 DOI: 10.1016/j.gie.2012.12.006]
62 **Chiu P**, Inoue H, Teoh A, Inoue H, Teoh A, Wong S, Ng E. Per oral endoscopic myotomy for treatment of hypertensive lower esophageal sphincter [abstract]. *Gastrointest Endosc* 2011; **73** Suppl 4: AB107 [DOI: 10.1016/j.gie.2011.03.1187]
63 **Khashab MA**, Saxena P, Kumbhari V, Nandwani M, Roland BC, Stein E, Clarke JO, Stavropoulos S, Inoue H, Pasricha PJ. Peroral endoscopic myotomy as a platform for the treatment of spastic esophageal disorders refractory to medical therapy (with video). *Gastrointest Endosc* 2014; **79**: 136-139 [PMID: 24342590 DOI: 10.1016/j.gie.2013.08.021]
64 **Teitelbaum EN**, Soper NJ, Arafat FO, Santos BF, Kahrilas PJ, Pandolfino JE, Hungness ES. Analysis of a learning curve and predictors of intraoperative difficulty for peroral esophageal myotomy (POEM). *J Gastrointest Surg* 2014; **18**: 92-98; discussion 98-99 [PMID: 24002767 DOI: 10.1007/s11605-013-2332-0]
65 **Maselli R**, Inoue H, Misawa M, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Suzuki K, Kudo S. Peroral endoscopic myotomy (POEM) in a 3-year-old girl with severe growth retardation, achalasia, and Down syndrome. *Endoscopy* 2012; **44** Suppl 2 UCTN: E285-E287 [PMID: 22933258 DOI: 10.1055/s-0032-1309924]
66 **Chen WF**, Li QL, Zhou PH, Yao LQ, Xu MD, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Hu JW, Cai MY, He MJ, Cui Z. Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study. *Gastrointest Endosc* 2015; **81**: 91-100 [PMID: 25088923 DOI: 10.1016/j.gie.2014.06.035]

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MINIREVIEWS

Examining the whole bowel, double balloon enteroscopy: Indications, diagnostic yield and complications

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Abstract

Double balloon enteroscopy (DBE) is an advanced type of endoscopic procedure which brings the advantage of reaching the whole small bowel using anterograde or the retrograde route. This procedure is both diagnostic and interventional for a variety of small intestinal diseases, such as vascular lesions, tumors, polyps and involvement of inflammatory bowel diseases. Main indication is the diagnosis and treatment of mid-gastrointestinal bleeding according to the recent published data all over the world. The complication rates seem to be higher than conventional procedures but growing experience is lowering them and improving the procedure to be safe and well tolerated. This review is about the technique, indications, diagnostic importance and complications of DBE according to the literature growing since 2001.

Key words: Endoscopy; Small bowel; Double balloon enteroscopy

Core tip: Double balloon enteroscopy (DBE) is a novel technique of great interest as the clinician gains the opportunity of examining the whole small bowel without any surgical intervention. Diagnostic and therapeutic ability of the procedure influences the importance and common use of DBE for patients with documented or suspected small bowel disease. This review summarizes the indications, diagnostic yield and complications of the procedure according to the worldwide knowledge since 2001.

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INTRODUCTION

Evolving fiber optic technology provided the opportunity of examining inner body compartments that can be reached through either a natural or an artificial orifice. Gastrointestinal (GI) endoscopy is one of the best

modalities to perform further investigations for the patients with digestive complaints. However before 1980s due to lack of technological improvements physicians had chance to examine only a short portion of the GI tract. Luckily only esophagogastroduodenoscopy and colonoscopy had the ability to diagnose and treat most of GI disturbances as we still experience in our daily practice that diseases associated with small bowel are comparably less to ones that involve upper GI and colon. The initial technique for small bowel endoscopy is push enteroscopy which was needed to be improved due to restricted capability of investigation depth. Single and double balloon enteroscopy (DBE) are now better procedures with improved visualization capability that gives physicians to examine the whole small bowel. By combining either upper or lower GI investigations now we have the opportunity to visualize the whole GI tract. These novel types of endoscopic procedures increase the effectiveness of diagnosis and minimally invasive treatments of small bowel and reduce the need for surgical interventions. This review aims to summarize indications, clinical importance and complications of DBE.

Figure 1 Double balloon system, the tip and overtube.

REVIEW

Technical information

DBE system consists of a high-resolution video endoscope, with a working length of 200 cm and a flexible overtube made of polyurethane. Latex balloons are attached at the tip of the endoscope and also on the overtube, and can be filled with air or emptied using a pressure controlled pump. The principle of the DBE technique is based on alternating pushing and pulling maneuvers, in order to place the small bowel segments onto the overtube step by step[1]. DBE can be performed *via* oral or anal route according to the clinical decision. Twelve hours of food and approximately 4 h of clear liquid fasting will be enough for the patient preparation of oral DBE. However standard colonoscopy preparation with restricted diet and laxatives will be needed for retrograde examination[2]. Peroperative sedation is necessary as the procedure duration is long and lower patient tolerance is expected to disturb the success of the procedure. Many options can be used for sedation but conventional conscious sedation with propofol is mainly used. Deep monitored sedation (with propofol, midazolam and/or fentanyl) can be preferred for oral examination with prolonged duration of the procedure[3]. Radiologic fluoroscopic assistance can be used according to the endoscopist's preference. The goal of the procedure is to examine the whole small bowel from duodenum to caecum or vice versa. However total enteroscopy can be performed in approximately 20% to 70% of the patients. Using both routes (oral and anal) complementary to each other by signing the furthest depth by tattooing or clip application, increases total enteroscopy rates. 230 cm beyond Treitz and 135 cm proximal to ileocecal valve can be considered as the average insertion depths for oral and anal route according to many different case series in the literature (Figure 1).

Indications of DBE

The indications of DBE mainly consist of similar pathologies of upper and lower GI system that are localized or suspected to be in the small intestine. As the procedure takes long time and is an advanced and hard intervention, it is mostly indicated after some initial investigations. The indications and some interventions due to diagnosis are summarized on Table 1.

Mid-GI bleeding

The most common indication (up to half of the procedures) for DBE is suspected or known mid-GI bleeding which refers to the blood loss from the distance between papilla Vateri and ileocecal valve. This can be either occult or obscure which may suggest an idea to choose the beginning route for the procedure, where melena encourages the oral route, the occurrence of hematochesia which cannot be defined by routine colonoscopy suggests retrograde examination for the initial management[4,5]. Video capsule endoscopy (VCE) is mostly the first choice to investigate occult mid-GI bleeding and after diagnosis of bleeding site or determining the need for additional intervention DBE is performed as a completing procedure[6]. DBE has up to 90% of diagnostic yield

Table 1 Indications and Interventions in double balloon enteroscopy

Indications	Therapeutic interventions
Mid-gastrointestinal bleeding	Endoscopic hemostatic therapies Injection sclerotherapy Argon plasma coagulation Endoscopic hemostatic clip application
Abnormal findings in other examinations	Diagnosis and therapy
Polyps of the small bowel (*e.g.*, polyposis syndromes)	Endoscopic polypectomy
Crohn's diseases	Diagnostic sampling
Diagnosis, complications	Balloon dilatation for strictures
Foreign body ingestion	Foreign body removal
Small bowel tumors	Diagnostic sampling Self-expanding stents for obstruction
Endoscopic retrograde cholangiography in surgically altered anatomy	Diagnosis Stone extraction Dilatation Stenting
Incomplete colonoscopy due to technical difficulty	Complete colonoscopy

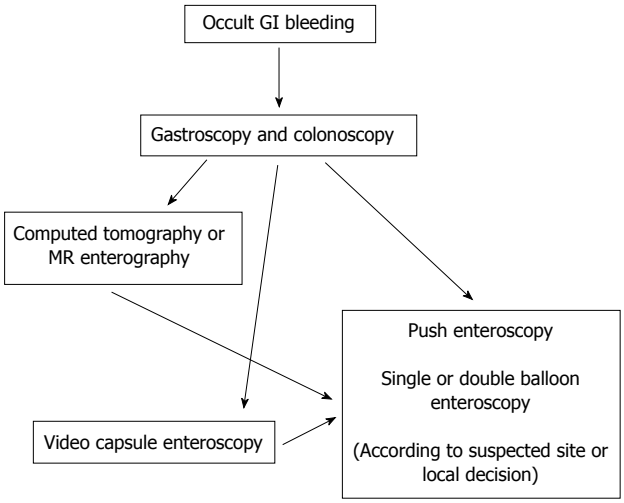

Figure 2 Algorithm for suspected occult gastrointestinal bleeding. Radiological imaging or video capsule endoscopy can be used for initial addressing the focus and enteroscopy (suitable route and modality) can be used for definitive diagnosis and therapeutic intervention. GI: Gastrointestinal; VCE: Video capsule endoscopy; MR: Magnetic resonance.

for mid GI bleeding which is comparable to VCE and significantly better than push enteroscopy as having the advantage of improved insertion depth[7]. As an alternative, push enteroscopy has been proven to have a diagnostic yield from 12% to 80% in investigating mid-GI bleeding, and higher rates are achieved when the bleeding is obscure (Figure 2).

Beyond diagnostic accuracy DBE brings the advantage of therapeutic interventions and ability to obtain tissue samples which is a great advantage when compared to VCE[8]. Clinician can perform endoscopic hemostatic techniques for bleeding sites at the time of diagnosis even documented initially with another

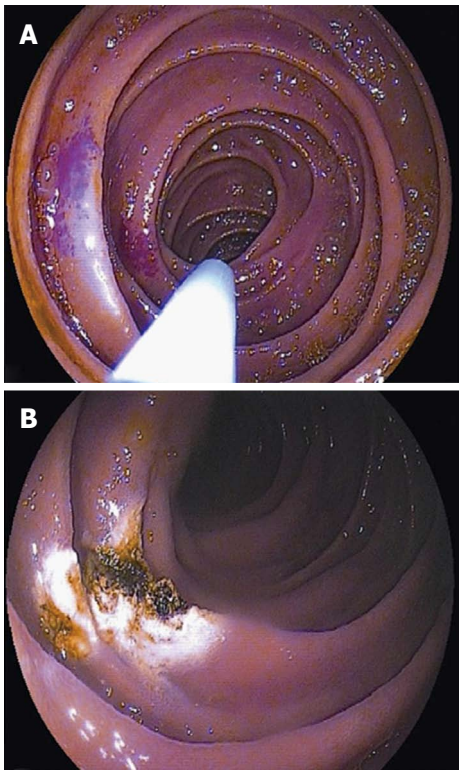

Figure 3 Double balloon enteroscopy. A: Endoscopic appearance of an angioectasia in mid jejunum; B: Eradication of angioectasia with Argon Plasma Coagulation application.

examination (*i.e.*, radiological, scintigraphic or angiographic) or not. Also lesions that cause bleeding (*i.e.*, angiodysplasia, polyps, small bowel tumors, foreign bodies...) diagnosed by using VCE can be reached with DBE for further tissue sampling or therapeutic interventions[9,10]. When the bleeding is severe and persistent or the probability of intervention is strong, DBE can take the first place instead of VCE (Figure 3).

Abnormal findings in other examinations

The interventional advantage offers DBE to be performed after abnormal findings of an initial diagnostic modality. Computed tomography (CT), magnetic resonance imaging (MRI) and VCE findings with suspected lesions can be confirmed and further applications can be performed with DBE. Also with suspected or known strictures of the small bowel, DBE comes further than VCE in order to avoid retention of the capsule and DBE becomes the initial approach for the patient[8].

Polyposis syndromes

The use of DBE in polyposis syndromes such as Familial Adenomatous Polyposis and Peutz Jeghers syndrome can be for screening and interventions for symptomatic patients (*i.e.*, bleeding or partial obstruction)[11]. Polyps larger than 15 mm are considered to bring tendency to intussusception and are recommended to be removed. VCE is mainly used for detecting the large polyps or for surveillance, but DBE is encouraged to be performed

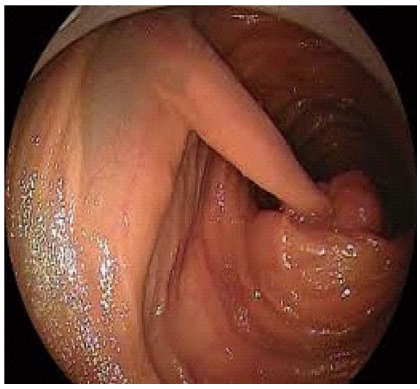

Figure 4 Jejunal polyp of Peutz-Jeghers syndrome.

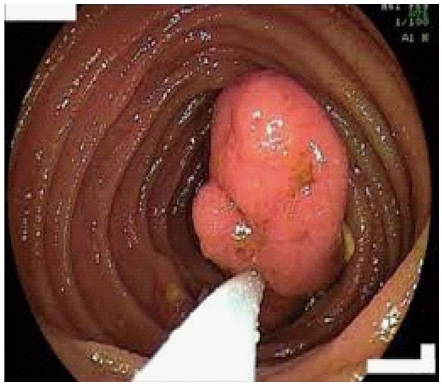

Figure 5 Polypectomy with double balloon enteroscopy.

for polypectomy instead of surgery. Patients with obstruction are treated with surgery and most of these patients that underwent surgery have intraabdominal adhesions. The risk of getting stuck and iatrogenic obstruction with capsule itself limits the use of CE in this setting and DBE becomes mainly the first choice for even surveillance of the small bowel. The opportunity for polypectomy and mechanical dilatation of the intestinal strictures are the other unique advantages of DBE against other diagnostic tools[12] (Figures 4 and 5).

Crohn's disease

DBE is not the first choice for the diagnosis of Crohn's disease (CD), but suspicion of the disease with only small bowel involvement and follow up of the strictures to confirm even inflammatory or fibrotic to modify the treatment of the patient would bring the need for using DBE in the diagnostic side of this disease. Also tissue sampling for suspected malignancy on CD and ability to dilate the strictures in the small bowel other implementations of DBE in CD[13]. Endoscopic confirmation of strictures to be inflammatory or fibrotic is of great importance to steer the treatment. Inflammatory strictures are suitable candidates for medical therapy where fibrotic strictures need mechanical interventions such as dilatation or surgery.

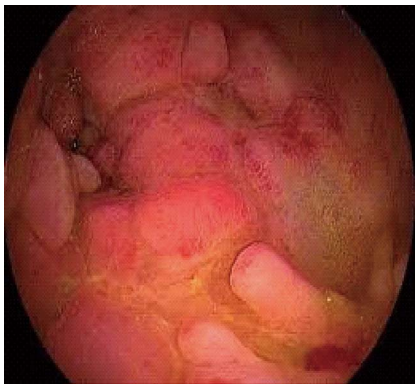

Figure 6 Jejunal stricture of Crohn's disease.

Endoscopic dilatation therapy is an option for short (< 3-4 cm), fibrotic strictures mainly due to scar tissues. The recurrence of strictures and need for repetitive dilatation or surgery is observed in a wide range and this information needs further investigations to be determined[14] (Figure 6).

Foreign body removal

Ligament of Treitz is one of the anatomical narrow points where the intestinal passage is relatively altered. However foreign bodies may pass this anatomical site and reach small bowel easily. The foreign bodies that are beyond the reach of gastroscopy and colonoscopy are candidates for DBE. Foreign bodies can be observed in pathologically narrowed intestinal sites such as tumors, strictures and large polyps. Even wireless capsules used for VCE can get stuck and need to be removed with DBE. Potentially harmful foreign bodies such as needles can be safely removed by using DBE with the help of overtube.

Small bowel tumors

Suspected small bowel lymphoma in Celiac disease and a solitary mass of small bowel documented in an initial diagnostic procedure can be the indication to perform DBE. As small bowel tumors can be seen nearly 5% of patients with mid GI bleeding, direct visualization of the lesion and histologic sampling before surgical intervention is crucial and DBE is the choice of initial procedure[15]. Also tattooing with DBE prior to surgery would be useful for surgeons to perform the most suitable surgical design (Figure 7).

Biliary interventions in surgically modified GI tract

DBE gives clinicians the chance to perform endoscopic retrograde cholangiopancreatography in patients with Bilroth Ⅱ and Roux-en-Y anastomosis who have altered anatomy due to surgery. This approach can be both diagnostic or interventional such as stone extraction, dilatation or biliary stenting. Also patients who underwent bariatric surgery and gastric bypass have a long descending small bowel loop that lead

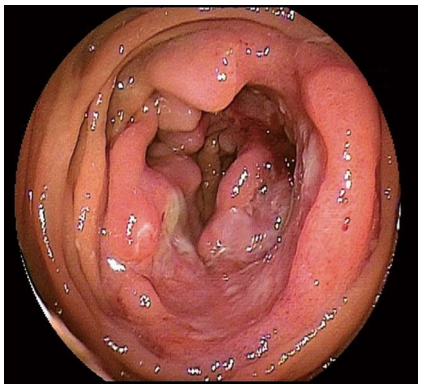

Figure 7 Ulcerating tumor located in mid jejunum.

to the afferent loop which can obtain access to the duodenum or the gastric remnant. DBE is used to pass this prolonged route in order to reach the biliary system.

DBE can also be used in patients who could not have complete ileocolonoscopy due to technical difficulties such as adhesions.

Complications

Procedure related complications differ according to the content of the examination. A procedure without therapeutic intervention brings low rates of complications. Due to prolonged procedure and air insufflation, abdominal pain can be observed in up to 20% patients. Acute pancreatitis with a rate of 0.3%-0.4% is the most common complication for oral route. It is supposed to be the result of increased pressure at the site of major papilla and ischemia of pancreas due to push and pull maneuvers. When therapeutic intervention is used complication rates increase up to 10% (perforation or bleeding following polypectomy or mucosal resection)[9,13,16]. Patients who had previous abdominal surgery and altered anatomy has greater risk of complications. Also prolonged sedation beyond from the procedure itself has the risk of respiratory depression and aspiration with a rate of 1%. Experience of the endoscopist, shorter time of procedure and inflating the balloons distal to Treitz ligament are the clues to reduce the rate of complications.

Contraindications of DBE

The contraindications for DBE are the same as conventional upper or lower GI endoscopic procedures. These are presence of shock, acute myocardial infarction, fulminant colitis, acute perforation and peritonitis. Intraabdominal adhesions increase the difficulty of the procedure and limit the depth of insertion but they are not counted as a contraindication.

Alternative techniques to examine the small bowel

VCE is a good alternative or an initial procedure to use as a diagnostic tool mainly investigating mid-GI bleeding. However the inability of intervention is the main drawback of VCE. Three meta-analyses in the literature of DBE *vs* VCE showed similar diagnostic yields in patients with obscure GI bleeding[17-19]. A retrospective study of 162 patients demonstrated an advantage of VCE where it is technically hard to reach with DBE and superiority of DBE in patients with Roux-en-Y loop anatomy and diverticula. Overall, the diagnostic yield for DBE *vs* VCE appears to be similar. VCE has the advantage of being noninvasive and is more likely to achieve complete small bowel enteroscopy. As VCE can be performed in outpatient setting without sedation it does not carry the additional risks of anesthesia.

In most clinical scenario the initial approach is VCE and after addressing the site of pathology DBE is used for sampling or therapeutic intervention. This sequential approach decreases the procedure duration and enhances interventional success.

Single balloon enteroscopy (SBE) is another alternative procedure for similar indications with similar capabilities. Limited number of trials that compare SBE and DBE have showed that they have similar diagnostic and therapeutic yield. However DBE seems to be more effective in performing complete enteroscopy[20-23].

Intraoperative enteroscopy (IOE) is an another alternative but after development of balloon enteroscopy techniques, IOE is not of initial choice as it is incomparably invasive.

CONCLUSION

DBE was first introduced by Yamamoto *et al*[1] In 2001. Evolving technologic advances and experience of the clinicians has made this particularly difficult procedure to be highly effective and safe for evaluation of the small bowel[24]. Growing experience more than a decade provided the chance to examine the whole intestinal system *via* oral or rectal route. DBE has reduced the need of surgery for small intestinal diseases. Despite its high diagnostic yield the complications of the procedure are reasonable and can be reduced with experience and basic precautions. Despite the easy use of VCE DBE will remain an important small intestinal examination as it has the ability of therapeutic intervention and tissue sampling. Cumulative experience of the endoscopist increase the success and insertion depth when reducing the complications and duration of the procedure. This knowledge suggest that DBE should be best performed in referral centers by educated endoscopists. Also use of carbon dioxide insufflation instead of ambient air increases insertion depth and patient tolerance during the procedure[25,26].

REFERENCES

1 **Yamamoto H**, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K. Total enteroscopy with a nonsurgical steerable

double-balloon method. *Gastrointest Endosc* 2001; **53**: 216-220 [PMID: 11174299 DOI: 10.1067/mge.2001.112181]
2 **Gerson LB**, Flodin JT, Miyabayashi K. Balloon-assisted enteroscopy: technology and troubleshooting. *Gastrointest Endosc* 2008; **68**: 1158-1167 [PMID: 19028224 DOI: 10.1016/j.gie.2008.08.012]
3 **Choi H**, Choi KY, Eun CS, Jang HJ, Park DI, Chang DK, Kim JO, Ko BM, Lee MS, Huh KC, Han DS, Byeon JS, Yang SK, Kim JH. Korean experience with double balloon endoscopy: Korean Association for the Study of Intestinal Diseases multi-center study. *Gastrointest Endosc* 2007; **66**: S22-S25 [PMID: 17709024 DOI: 10.1016/j.gie.2007.06.048]
4 **Sun B**, Rajan E, Cheng S, Shen R, Zhang C, Zhang S, Wu Y, Zhong J. Diagnostic yield and therapeutic impact of double-balloon enteroscopy in a large cohort of patients with obscure gastrointestinal bleeding. *Am J Gastroenterol* 2006; **101**: 2011-2015 [PMID: 16848814 DOI: 10.1111/j.1572-0241.2006.00664.x]
5 **May A**, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. *Gastrointest Endosc* 2005; **62**: 62-70 [PMID: 15990821 DOI: 10.1016/S0016-5107(05)01586-5]
6 **Pohl J**, Delvaux M, Ell C, Gay G, May A, Mulder CJ, Pennazio M, Perez-Cuadrado E, Vilmann P. European Society of Gastrointestinal Endoscopy (ESGE) Guidelines: flexible enteroscopy for diagnosis and treatment of small-bowel diseases. *Endoscopy* 2008; **40**: 609-618 [PMID: 18612948 DOI: 10.1055/s-2008-1077371]
7 **Heine GD**, Hadithi M, Groenen MJ, Kuipers EJ, Jacobs MA, Mulder CJ. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. *Endoscopy* 2006; **38**: 42-48 [PMID: 16429354 DOI: 10.1055/s-2005-921188]
8 **Nakamura M**, Niwa Y, Ohmiya N, Miyahara R, Ohashi A, Itoh A, Hirooka Y, Goto H. Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in patients with suspected small-bowel bleeding. *Endoscopy* 2006; **38**: 59-66 [PMID: 16429356 DOI: 10.1055/s-2005-870446]
9 **Xin L**, Liao Z, Jiang YP, Li ZS. Indications, detectability, positive findings, total enteroscopy, and complications of diagnostic double-balloon endoscopy: a systematic review of data over the first decade of use. *Gastrointest Endosc* 2011; **74**: 563-570 [PMID: 21620401 DOI: 10.1016/j.gie.2011.03.1239]
10 **Chen WG**, Shan GD, Zhang H, Li L, Yue M, Xiang Z, Cheng Y, Wu CJ, Fang Y, Chen LH. Double-balloon enteroscopy in small bowel tumors: a Chinese single-center study. *World J Gastroenterol* 2013; **19**: 3665-3671 [PMID: 23801870 DOI: 10.3748/wjg.v19.i23.3665]
11 **Akarsu M**, Uğur Kantar F, Akpinar H. Double-balloon endoscopy in patients with Peutz-Jeghers syndrome. *Turk J Gastroenterol* 2012; **23**: 496-502 [PMID: 23161293 DOI: 10.4318/tjg.2012.0356]
12 **Jovanovic I**, Vormbrock K, Zimmermann L, Djuranovic S, Ugljesic M, Malfertheiner P, Fry LC, Mönkemüller K. Therapeutic double-balloon enteroscopy: a binational, three-center experience. *Dig Dis* 2011; **29** Suppl 1: 27-31 [PMID: 22104749 DOI: 10.1159/000331125]
13 **Schulz C**, Mönkemüller K, Salheiser M, Bellutti M, Schütte K, Malfertheiner P. Double-balloon enteroscopy in the diagnosis of suspected isolated Crohn's disease of the small bowel. *Dig Endosc* 2014; **26**: 236-242 [PMID: 23855454 DOI: 10.1111/den.12142]
14 **Möschler O**, May A, Müller MK, Ell C. Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. *Endoscopy* 2011; **43**: 484-489 [PMID: 21370220 DOI: 10.1055/s-0030-1256249]
15 **Onal IK**, Akdogan M, Arhan M, Yalinkilic ZM, Cicek B, Kacar S, Kurt M, Ibis M, Ozin YO, Sayilir A, Sayilir A, Sasmaz N. Double balloon enteroscopy: a 3-year experience at a tertiary care center. *Hepatogastroenterology* 2012; **59**: 1851-1854 [PMID: 22819903 DOI: 10.5754/hge10828]
16 **Van Assche G**, Vermeire S, Rutgeerts P. Endoscopic therapy of strictures in Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 356-358; discussion 356-358 [PMID: 17230480 DOI: 10.1002/ibd.20091]
17 **Chen X**, Ran ZH, Tong JL. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. *World J Gastroenterol* 2007; **13**: 4372-4378 [PMID: 17708614 DOI: 10.3748/wjg.v13.i32.4372]
18 **Pasha SF**, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, Sharma VK. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2008; **6**: 671-676 [PMID: 18356113 DOI: 10.1016/j.cgh.2008.01.005]
19 **Teshima CW**, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. *J Gastroenterol Hepatol* 2011; **26**: 796-801 [PMID: 21155884 DOI: 10.1111/j.1440-1746.2010.06530.x]
20 **Arakawa D**, Ohmiya N, Nakamura M, Honda W, Shirai O, Itoh A, Hirooka Y, Niwa Y, Maeda O, Ando T, Goto H. Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. *Gastrointest Endosc* 2009; **69**: 866-874 [PMID: 19136098 DOI: 10.1016/j.gie.2008.06.008]
21 **May A**, Färber M, Aschmoneit I, Pohl J, Manner H, Lotterer E, Möschler O, Kunz J, Gossner L, Mönkemüller K, Ell C. Prospective multicenter trial comparing push-and-pull enteroscopy with the single- and double-balloon techniques in patients with small-bowel disorders. *Am J Gastroenterol* 2010; **105**: 575-581 [PMID: 20051942]
22 **Domagk D**, Mensink P, Aktas H, Lenz P, Meister T, Luegering A, Ullerich H, Aabakken L, Heinecke A, Domschke W, Kuipers E, Bretthauer M. Single- vs. double-balloon enteroscopy in small-bowel diagnostics: a randomized multicenter trial. *Endoscopy* 2011; **43**: 472-476 [PMID: 21384320 DOI: 10.1055/s-0030-1256247]
23 **Takano N**, Yamada A, Watabe H, Togo G, Yamaji Y, Yoshida H, Kawabe T, Omata M, Koike K. Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial. *Gastrointest Endosc* 2011; **73**: 734-739 [PMID: 21272875 DOI: 10.1016/j.gie.2010.10.047]
24 **Delvaux M**, Gay G. International Conference on Capsule and Double-Balloon Endoscopy (ICCD). Paris, 27-28 August 2010. *Endoscopy* 2011; **43**: 533-539 [PMID: 21425038 DOI: 10.1055/s-0030-1256248]
25 **Domagk D**, Bretthauer M, Lenz P, Aabakken L, Ullerich H, Maaser C, Domschke W, Kucharzik T. Carbon dioxide insufflation improves intubation depth in double-balloon enteroscopy: a randomized, controlled, double-blind trial. *Endoscopy* 2007; **39**: 1064-1067 [PMID: 18072057 DOI: 10.1055/s-2007-966990]
26 **Hirai F**, Beppu T, Nishimura T, Takatsu N, Ashizuka S, Seki T, Hisabe T, Nagahama T, Yao K, Matsui T, Beppu T, Nakashima R, Inada N, Tajiri E, Mitsuru H, Shigematsu H. Carbon dioxide insufflation compared with air insufflation in double-balloon enteroscopy: a prospective, randomized, double-blind trial. *Gastrointest Endosc* 2011; **73**: 743-749 [PMID: 21237455 DOI: 10.1016/j.gie.2010.10.003]

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MINIREVIEWS

Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of kidney lesions: A review

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Abstract

Traditionally, treatment of renal lesions is indicated based only on imaging features. Although controversy exists about tissue sampling from small renal masses, renal biopsy is indicated in some cases. In this review, we discuss the rationale for endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and summarize the recent advances in this field, providing recommendations for the practicing clinician. The use of EUS-FNA appears to be a safe and feasible means of confirming or excluding malignancy. EUS allows assessment and biopsy of masses or lesions within both kidneys and related complications are rare. The main advantages of EUS-FNA are that it can be done as an outpatient procedure, with good results, minimal morbidity and a short hospital stay. Nevertheless, EUS-FNA of renal masses should be indicated only in selected cases, in which there is potential to decrease unnecessary treatment of small renal masses and to best select tumors for active surveillance and minimally invasive ablative therapies. Additionally, some renal lesions may be ineligible for EUS-guided biopsy because of anatomical limitations. EUS-FNA renal biopsy will probably be best applied to central anterior renal masses, while tumors on the posterior aspect of the kidney, percutaneous access will probably be superior.

Key words: Kidney; Renal; Endoscopic ultrasound; Cancer; Puncture

Core tip: Although controversy exists on the need of renal biopsy, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be used in selected cases. In this review we discuss the rationale for EUS-FNA kidney and summarize the recent advances in this field, providing recommendations for the practicing clinician.

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INTRODUCTION

Improvements on imaging technology and widespread use of imaging studies have not only increased the detection, but also allowed better characterization of incidental renal masses, which resulted in smaller lesions being depicted on such studies[1]. Up to 80% of renal cell carcinomas (RCC) are incidentally detected during radiological work-up, usually for non-urological indications. At time of nephrectomy, 70%-90% of solid renal lesions prove to be RCC[2,3], accounting for 2% of all cancers and being the leading kidney malignancy[2,4,5]. Therefore, an enhancing renal neoplasm on computed tomography (CT) or magnetic resonance imaging (MRI) has been considered by most urologists to be a sufficient indication for surgery because about 80% of such lesions prove to be RCC.

Some recent studies demonstrated that up to 30% of detected renal lesions are benign at surgery, depending on renal lesion size[6,7]. Furthermore, current management of small renal tumors involves from surveillance strategies to alternative minimally invasive and nephron-sparing options, such as laparoscopic/robotic partial nephrectomy, cryotherapy and radiofrequency ablation. In this scenario, pre-therapeutic guided biopsy might be helpful to avoid unnecessary surgery and to choose the most appropriate management strategy. In almost 30% of selected patients, a surgical procedure became non-mandatory after renal biopsy results were obtained[8]. Therefore, if a renal biopsy might impact treatment decisions, the use of core biopsy and fine needle aspiration (FNA) for better characterization of suspicious renal masses preoperatively should be considered.

In most patients, treatment of renal lesions is indicated based on imaging features alone. Although controversy exists about tissue sampling from small renal masses (tumors with less than 4 cm, since they have up to 30% chance of being benign), renal biopsy is indicated to: (1) characterize radiographically indeterminate lesions; (2) confirm malignancy in patients, who either are not surgical candidates or plan primary treatment with minimally invasive ablative therapy; and (3) rule out non-renal cell primary tumors (metastasis and lymphoma) or benign conditions (abscess), which may not require surgery[9-11].

Biopsy has also been used to confirm the diagnosis and the histological subtype of a renal primary lesion in patients with disseminated metastasis or unresectable retroperitoneal mass. In metastatic RCC, patients with clear cell subtype histology are most likely to benefit from adjuvant immunotherapy following cytoreductive nephrectomy. Additionally, new target therapies demonstrate variant response rates with distinctive RCC subtypes[2,8].

Tissue sampling of renal lesions is traditionally performed by using percutaneous sonographic or CT guidance. The use of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is infrequently performed for the evaluation for RCC and there are few reported studies addressing the safety and feasibility of this technique[2,8,11-14], as shown in Table 1.

The objective of this review is to: (1) outline the rationale for EUS-FNA kidney; (2) detail the procedural technique; (3) evaluate the clinical outcomes and limitations of the method; and (4) provide recommendations for the practicing clinician.

RATIONALE FOR EUS-FNA OF KIDNEY LESIONS

Since EUS initial report in the 1980s, it rapidly crawled from a pure imaging modality used mainly for diagnostic purposes, especially for lesions of digestive tract, to a more interventional and therapeutic application[15]. With the subsequent advent of FNA, this technique has became the gold-standard procedure for the assessment of benign and malignant diseases of the gastrointestinal tract and of adjacent organs[16,17]. EUS-FNA is highly accurate, sensitive and specific with estimates reaching 80%, 90% and 100%, respectively for cytological diagnosis[18-20].

As discussed above, percutaneous renal mass biopsy must not be performed for renal lesions less than 40 mm but it should be indicated for incompletely accurate renal imaging diagnosis after a full imaging evaluation. As well, EUS-FNA cannot currently be recommended as routine for cytologic diagnosis of renal masses, however, it might be useful in the aforementioned clinical situations when a renal biopsy should have an impact on clinical decision, especially for central and anterior renal masses. The advantages of a EUS-FNA in these cases is the potential to decrease unnecessary treatment of small renal masses and to best select renal tumors for active surveillance and minimally invasive ablative therapies[12,21]. EUS-FNA appears to be a safe and cost-effective way of confirming or excluding malignancy and may hinder the need for CT-guided exams[2].

PROCEDURAL TECHNIQUE

Anatomic approximation to both kidneys allows access for tissue sampling with the echoendoscope positioned in the upper gastrointestinal (GI) tract. Translating the probe within the duodenum or stomach, with the extension of 12.5 cm for 7.5 MHz probe, is sufficient to visualize both kidneys. The right kidney can be readily imaged by locating the transducer in the second portion of the duodenum (green area Figure 1) and rotating laterally, and the left kidney can be visualized when the transducer is facing posterolaterally into the body of the stomach (grey area Figure 1A)[12]. Color doppler ultrasound can verify the presence of major trespassing vascular structures, which should be identified and avoided during FNA.

Table 1 Reported endoscopic ultrasound-guided fine needle aspiration case series

Ref.	Design	Location	Mean size	Approach	No. of EUS-FNA	Technical success	Complications
Farrell *et al*[2]	Case report	Right kidney	9 cm	Duodenum 22 G needle 2 passes	1	100%	No
Eloubeidi *et al*[13]	Prospective study	N/A	N/A	N/A 22 G needle up to 5 passes	1	N/A	N/A
Artifon *et al*[12]	Case report	Left kidney	1.3 cm	Gastric body 22 G needle 3 passes	1	100%	No
DeWitt *et al*[11]	Case series	Right kidney (n = 5) Left kidney (n = 10)	3.2 cm (1.1-6 cm)	Duodenum for right kidney and gastric body for left kidney 22 G needle 2 - 4 passes	15	80% (12/15)	No
Lakhtakia *et al*[14]	Case report	Right kidney	1.5 cm	Duodenum 22 G needle N/A passes	1	100	Transient hematuria
Moura *et al*[8]	Case series	Right kidney (n = 4) Left kidney (n = 4) Bilateral (n = 1)	6 cm (1.3-16 cm)	Duodenum for right kidney and gastric body for left kidney 22 G needle 3 passes	10	90% (9/10)	No

EUS-FNA: Echoendoscopic ultrasonographic fine needle aspiration; N/A: Non available.

EUS-FNA is performed (Figure 1B) using curvilinear array echoendoscopes that are produced by three leading manufacturers: Olympus (Olympus Medical Systems Inc., Tokyo, Japan), Pentax (Pentax, Tokyo, Japan) and Fujinon (Fujifilm Corp., Tokyo, Japan). The working channel must be at least of 2.8 mm to accept the FNA needle and the echoendoscopes present at an elevator located on the side of the scope at the tip portion, that is able to make changes in the exit angle of the FNA needle to facilitate the targeting process[15].

Needles for renal EUS-FNA are currently available in 3 sizes (19, 22 and 25 gauge). Thinner needles are used to gather cytological specimens, while thicker needle are better applied for acquisition of a tissue specimen for histological examination, that can be more useful to reach the definitive diagnosis. The choice of the needle depends on the type and site of the lesion to be sampled. In all the studies listed in Table 1, the kidney was punctured using a 22-gauge needle. More data is probably needed to characterize the correct needle size depending to the type and location of the lesion.

Whenever possible, EUS-FNA should be done under deep sedation with the assistance of an anesthesiologist. The main advantages of EUS-FNA are that it can be done as an outpatient procedure, and it appears to be safe with good results, minimal morbidity and a short hospital stay, as demonstrated in Table 1.

PROCEDURAL LIMITATIONS

Some renal masses may be ineligible for EUS-guided biopsy because of anatomical limitations. EUS-FNA renal biopsy will probably be best applied to central anterior renal masses, while tumors on the posterior aspect of the kidney, percutaneous access will probably be superior. Among other reasons, these limitations are likely to restrict widespread application of EUS for this indication[11].

EUS-FNA related complications of kidney masses sampling are similar to those for aspiration of GI masses and include localized bleeding, infection, hematoma, hematuria, pneumothorax, and needle tract seeding[14]. The risk of complications associated with EUS-FNA spans from less than 1% to 6%. Tracheal suction (5%), vomiting (0.3%), aspiration (0.3%), esophageal perforation and death (less than 0.06%) are reported complications of EUS. In a relatively small group of patients, the frequency of bleeding as a result of fine-needle aspiration of the kidney was 0.5%, whereas that associated with fine-needle aspiration of GI lesions was 1.3%[2].

Since the EUS needle has to transverse fewer tissue layers, the risk of needle seeding may be lower, with few cases reported. Overall, the prospect of needle track seeding is minor and it should be balanced against the benefit of a tissue diagnosis[12]. In a retrospective review of patients submitted to pancreatic mass FNA, either by EUS-FNA or percutaneous access, the incidence of peritoneal carcinomatosis was lower in the EUS-FNA group, which might suggest a lower risk of needle seeding[22].

Higher accuracy rates are achieved with on-site cytopathology examination to assess specimen adequacy that, however, is not available in all centers and may increase the cost of the procedure[15].

EUS-FNA is not done in situations when it is unlikely to alter the management of a cancer. In addition to the usual contraindications for any endoscopic

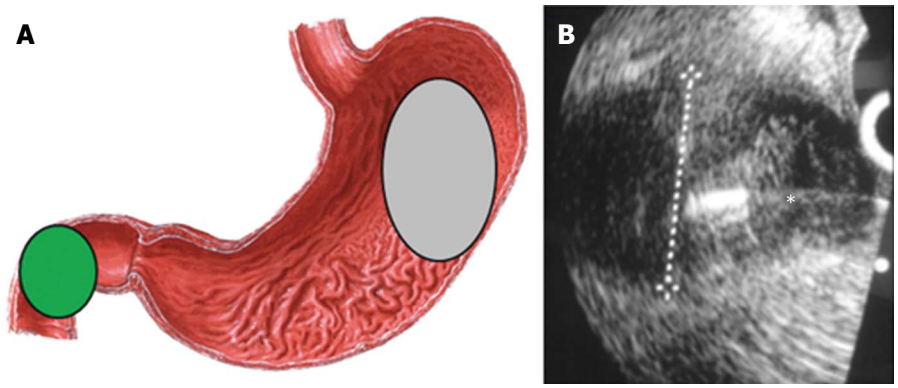

Figure 1 The right kidney image. A: Endoscopic ultrasound positioning and access for tissue sampling; B: Fine needle aspiration of a renal lesion. The asterix is over the needle to show the fine needle aspiration of the tumor.

procedure, including severe bleeding diathesis and thrombocytopenia, EUS-FNA is not advocated when good views of the lesion are not obtained or when a major vascular structure is present on the way to the target[15].

CONCLUSION

New techniques in EUS are emerging and will likely have a niche in aiding the diagnosis of undeterminate lesions. EUS allows visualization and sampling renal masses. This technique is evolving and will possibly have a role in diagnostic EUS in the future, as it appears to be a safe and feasible procedure with good results, minimal morbidity and a short hospital stay in the cases reported on the literature[2,8,11-13].

We recommend that EUS-FNA of renal masses should be indicated only in selected cases, in which the procedure may alter clinical management by avoiding unnecessary treatment and helping to select patients for active surveillance and minimally invasive ablative therapies. Further research should evaluate the benefits of preoperative renal biopsy use and randomization of percutaneous, laparoscopic and echoendoscopic approach should be compared.

REFERENCES

1 **Kutikov A**, Fossett LK, Ramchandani P, Tomaszewski JE, Siegelman ES, Banner MP, Van Arsdalen KN, Wein AJ, Malkowicz SB. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. *Urology* 2006; **68**: 737-740 [PMID: 17070344 DOI: 10.1016/j.urology.2006.04.011]

2 **Farrell JJ**, Brugge WR. EUS-guided fine-needle aspiration of a renal mass: an alternative method for diagnosis of malignancy. *Gastrointest Endosc* 2002; **56**: 450-452 [PMID: 12196796 DOI: 10.1016/S0016-5107(02)70062-X]

3 **Davis CJ**. Pathology of renal neoplasms. *Semin Roentgenol* 1987; **22**: 233-240 [PMID: 2825358]

4 **Sweeney JP**, Thornhill JA, Graiger R, McDermott TE, Butler MR. Incidentally detected renal cell carcinoma: pathological features, survival trends and implications for treatment. *Br J Urol* 1996; **78**: 351-353 [PMID: 8881940 DOI: 10.1046/j.1464-410X.1996.00140.x]

5 **Konnak JW**, Grossman HB. Renal cell carcinoma as an incidental finding. *J Urol* 1985; **134**: 1094-1096 [PMID: 4057398]

6 **Glassman D**, Chawla SN, Waldman I, Johannes J, Byrne DS, Trabulsi EJ, Gomella LG. Correlation of pathology with tumor size of renal masses. *Can J Urol* 2007; **14**: 3616-3620 [PMID: 17784981]

7 **Ozen H**, Colowick A, Freiha FS. Incidentally discovered solid renal masses: what are they? *Br J Urol* 1993; **72**: 274-276 [PMID: 8220985 DOI: 10.1111/j.1464-410X.1993.tb00716.x]

8 **Moura RN**, Lopes RI, Srougi M, Dall'oglio MF, Sakai P, Artifon EL. Initial experience with endoscopic ultrasound-guided fine needle aspiration of renal masses: indications, applications and limitations. *Arq Gastroenterol* 2014; **51**: 337-340 [PMID: 25591164]

9 **Renshaw AA**, Granter SR, Cibas ES. Fine-needle aspiration of the adult kidney. *Cancer* 1997; **81**: 71-88 [PMID: 9126135]

10 **Khan AA**, Shergill IS, Gujral SS, Timoney AG. Management of small indeterminate renal tumours: is there a case for needle biopsy? *BJU Int* 2007; **100**: 1-3 [PMID: 17433032 DOI: 10.1111/j.1464-410X.2007.06856.x]

11 **DeWitt J**, Gress FG, Levy MJ, Hernandez LV, Eloubeidi MA, Mishra G, Sherman S, Al-Haddad MA, LeBlanc JK. EUS-guided FNA aspiration of kidney masses: a multicenter U.S. experience. *Gastrointest Endosc* 2009; **70**: 573-578 [PMID: 19560139 DOI: 10.1016/j.gie.2009.04.006]

12 **Artifon EL**, Lopes RI, Kumar A, Lucon AM, Dall'oglio M, Hawan B, Sakai P, Srougi M. Endoscopic ultrasound facilitates histological diagnosis of renal cell cancer. *J Endourol* 2008; **22**: 2447-2450 [PMID: 19046085 DOI: 10.1089/end.2008.0151]

13 **Eloubeidi MA**, Tamhane A, Jhala N, Chhieng D, Jhala D, Crowe DR, Eltoum IA. Agreement between rapid onsite and final cytologic interpretations of EUS-guided FNA specimens: implications for the endosonographer and patient management. *Am J Gastroenterol* 2006; **101**: 2841-2847 [PMID: 17026562 DOI: 10.1111/j.1572-0241.2006.00852.x]

14 **Lakhtakia S**, Wee E, Gupta R, Anuradha S, Kalpala R, Monga A, Arjunan S, Reddy DN. Hematuria after endoscopic ultrasound-guided fine needle aspiration of a renal tumor in von Hippel-Lindau disease. *Endoscopy* 2012; **44** Suppl 2 UCTN: E133 [PMID: 22619034 DOI: 10.1055/s-0030-1256682]

15 **Trindade AJ**, Berzin TM. Clinical controversies in endoscopic ultrasound. *Gastroenterol Rep (Oxf)* 2013; **1**: 33-41 [PMID: 24759665 DOI: 10.1093/gastro/got010]

16 **Erickson RA**. EUS-guided FNA. *Gastrointest Endosc* 2004; **60**: 267-279 [PMID: 15278063]

17 **Tharian B**, Tsiopoulos F, George N, Pietro SD, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: Technique and applications in clinical practice. *World J Gastrointest Endosc* 2012; **4**: 532-544 [PMID: 23293723 DOI: 10.4253/wjge.v4.i12.532]

18 **Chang KJ**, Katz KD, Durbin TE, Erickson RA, Butler JA, Lin F, Wuerker RB. Endoscopic ultrasound-guided fine-needle aspiration.

Gastrointest Endosc 1994; **40**: 694-699 [PMID: 7859967]
19 **Vilmann P**, Hancke S, Henriksen FW, Jacobsen GK. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of lesions in the upper gastrointestinal tract. *Gastrointest Endosc* 1995; **41**: 230-235 [PMID: 7789681 DOI: 10.1016/S0016-5107(95)70343-8]
20 **Karadsheh Z**, Al-Haddad M. Endoscopic ultrasound guided fine needle tissue acquisition: where we stand in 2013? *World J Gastroenterol* 2014; **20**: 2176-2185 [PMID: 24605016 DOI: 10.3748/wjg.v20.i9.2176]
21 **Volpe A**, Kachura JR, Geddie WR, Evans AJ, Gharajeh A, Saravanan A, Jewett MA. Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy. *J Urol* 2007; **178**: 379-386 [PMID: 17561170]
22 **Micames C**, Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc* 2003; **58**: 690-695 [PMID: 14595302]

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Head mass in chronic pancreatitis: Inflammatory or malignant

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Abstract

Chronic pancreatitis increases the risk of developing pancreatic cancer. This often presents as a mass lesion in the head of pancreas. Mass lesion in the head of pancreas can also occur secondary to an inflammatory lesion. Recognising this is crucial to avoid unnecessary surgery. This is sometimes difficult as there is an overlap in clinical presentation and conventional computed tomography (CT) abdomen findings in inflammatory and malignant mass. Advances in imaging technologies like endoscopic ultrasound in conjunction with techniques like fine needle aspiration, contrast enhancement and elastography as well as multidetector row CT, magnetic resonance imaging and positron emission tomography scanning have been shown to help in distinguishing inflammatory and malignant mass. Research is ongoing to develop molecular techniques to help characterise focal pancreatic mass lesions. This paper reviews the current status of imaging and molecular techniques in differentiating a benign mass lesion in chronic pancreatitis and from malignancy.

Key words: Chronic pancreatitis; Pseudotumour; Imaging; Endoscopic ultrasonography; Molecular tool

Core tip: Evaluating head mass in chronic pancreatitis is clinically challenging. Advances in pancreatic imaging including endoscopic ultrasonography and molecular tools have been reviewed.

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INTRODUCTION

The risk of developing pancreatic cancer in patients with chronic pancreatitis is about fifteen times higher than in the average population[1]. A meta analysis has shown that 5% of the patients with chronic pancreatitis develop pancreatic cancer over a 20 year period[2]. About 70% of these tumours are located in the head

region of pancreas[3]. Patients with chronic pancreatitis also tend to develop inflammatory lesions in the head of pancreas which appears like tumour mass and is referred to as pseudotumour[4]. Confirming the diagnosis preoperatively is crucial because confusion may lead to either major pancreatic resection for benign disease or rejection of surgery for a potentially curable lesion.

Clinical features and biochemical parameters that suggest malignant mass in head of pancreas are older age, persistent jaundice, worsening abdominal pain, gastric outlet obstruction, significant weight loss and elevated CA 19:9 greater than 300 U/mL[5]. Conventional Imaging techniques like Ultrasound abdomen, CT and MRI provide useful information that helps in differentiating benign from malignant mass in head of pancreas[6]. Unfortunately, due to an overlap in clinical, biochemical and conventional imaging parameters, it is sometimes difficult to differentiate an inflammatory mass from cancer in head of pancreas[6]. This is supported by the fact that most large series of pancreatic resections for carcinoma head of pancreas show that 5%-10% of cases of inflammatory mass masquerade as pancreatic carcinoma[7,8].

The advent of endoscopic ultrasound (EUS) has been a major development in assessment of pancreatic disease including mass lesions in the head of pancreas[9]. High frequency EUS probes in the stomach located close to the pancreas, provide detailed images with no intervening bowel gas[9]. In addition, fine needle aspiration (FNA) performed for obtaining tissue sample further helps in diagnosis. New EUS based techniques like Digital Image analysis, EUS Elastography and Contrast enhanced EUS have shown promise in better characterisation of pancreatic mass lesion. In this paper we review the role of EUS in assessing pancreatic head mass in chronic pancreatitis and also briefly look at other radiological and molecular tools available for evaluation of this entity.

ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography has been found to be very useful in detecting small pancreatic mass lesions and has been shown to be better than other modalities for assessing vascular invasion and local spread[10,11]. EUS in association with other techniques like FNA or contrast enhancement has also been found to be useful in distinguishing benign from malignant pancreatic mass lesions. The data from studies evaluating the role of EUS in assessing pancreatic mass lesion has been summarised in Tables 1 and 2. Table 1 shows only studies which have included patients with background chronic pancreatitis. Most studies show that EUS alone is not capable of precisely differentiating between a pseudotumoral mass and carcinoma in the setting of chronic pancreatitis[12-14]. Presence of multilobularity, homogenous pattern, hyperechoic septa and Doppler signal within a lesion favour pseudotumour[12]. One of the limitations with EUS is the subjective nature of image assessment and performance which varies depending on experience. As the architectural changes are better detected by computer based methods than naked eye, it is possible that digital image analysis (DIA) obtained during EUS can remove the error of subjective assessment. Two studies with adequate number of subjects have shown that digital image analysis has sensitivity and specificity of above 90% in differentiating malignant and benign pancreatic mass lesion[15,16].

The limitations of conventional B mode EUS can be overcome by performing FNA which gives a tissue diagnosis. FNA is relatively safe as it does not traverse peritoneal cavity and avoids seeding of peritoneum. Unfortunately, FNA which has a sensitivity of above 90% in detecting pancreatic malignancy in pancreas with normal parenchyma, underperforms in the presence of chronic pancreatitis with sensitivity dropping to below 75%[12,17-19]. Vardarajulu and colleagues reported that in the 300 EUS FNA performed for pancreatic mass lesions, sensitivity was 91.3% in pancreas with normal parenchyma but only 73.9% when chronic pancreatitis was present[17]. Other studies have shown even poorer performance. In a study from Romania on 72 patients with Chronic Pancreatitis (17 had Pancreatic Carcinoma), EUS FNA had a sensitivity of only 50%[18]. Similarly, in another report from Germany on 13 patients with Chronic Pancreatitis and carcinoma, EUS FNA was able to detect carcinoma in only 7 of them[19]. Making more number of passes during FNA or repeating FNA may improve the yield[17,20].

Using molecular tools to detect mutation in tissue sample may be a useful adjunct to improve diagnostic yield[21-23]. Khalid *et al*[21], studied microsatellite markers and mutation in *K-ras* gene on EUS-FNA samples from patients with benign and malignant pancreatic masses. The mean fractional mutation rate was higher in pancreatic malignancy and use of molecular tool improved the diagnostic performance of FNA[21]. In another study from Czech Republic which included 101 subjects, mutations in *K-ras* and allelic loss in tumour suppressor genes were determined on EUS-FNA specimen[22]. Detection of mutation in *k-ras* gene, allelic loss of *p16* and *DPC4* gene improved the sensitivity of cancer detection to 100%[22]. A large prospective multicenter study which only looked at k-ras mutations in addition to cytopatholgy on FNA samples, found that assessing for *k-ras* mutation improved the diagnostic sensitivity for malignancy to 88% which was only marginally better than cytopathology alone (83%)[24]. However, absence of *K-ras* mutation was a strong indicator of benign lesion[24]. This study also highlights the importance of studying multiple markers rather than single one. Other studies have shown that absence of *k-ras* mutation in FNA samples from patients with chronic pancreatitis and mass lesion strongly suggest a benign lesion[24,25]. Data from the above studies suggest that molecular tests can play a significant role in diagnosing

Table 1 Endoscopic ultrasound in evaluating pancreatic mass lesions in patients with chronic pancreatitis

Ref.	Study subjects	Procedure	Outcome[1]
Fritscher-Ravens *et al*[19]	74 patients with focal pancreatic lesions and chronic pancreatitis	EUS FNA	Sn-54%
Vardarajulu *et al*[17]	75 patients with CP and focal pancreatic mass lesion	EUS FNA	Sn-73.9% Sp-100%
Iordache *et al*[18]	CP-55 CP and PC-17	EUS FNA	Sn-50% Sp-73.7%
Hocke *et al*[13]	86 patients with CP and pancreatic lesion	EUS CE-EUS	Sn-73.2% Sp-83.3% Sn-91.1% Sp-93.3%

[1]Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

pancreatic cancer in FNA samples and one should assess for k-ras mutations along with loss of tumour suppressor genes to improve yield.

Recent advances in EUS based technology like EUS Elastography, Contrast Enhanced EUS and computer software in interpreting images have shown promise in better characterisation of pancreatic mass lesions[26-28]. EUS elastography measures tissue stiffness[26,29]. The stiffness in malignant tumour is different from benign lesion or normal tissue and this is represented as different colour regions on the conventional real time EUS images. Usually blue colour indicates hard tissue, red suggests soft tissue and green represents tissue with intermediate stiffness. To remove subjective error, tissue strain can be quantitatively measured by software to provide strain ratios which are different for benign and malignant lesions[29,30]. The results of earlier studies with EUS elastography were disappointing showing low sensitivity and specificity[31,32]. This was probably due to fibrous architecture in both tumour and chronic pancreatitis[31]. Subsequent studies after the introduction of quantitative assessment methods including measurement of strain ratio have shown better outcomes (sensitivity > 90%)[30,33-35]. In a study measuring strain ratio during EUS elastography, ratio was 1.68 for normal pancreas, 3.38 for inflammatory mass and a very high ratio of 18.12 for pancreatic adenocarcinoma[30].

Contrast enhanced (CE) EUS makes use of injected contrast to assess vascularity of lesion and low mechanical index technique enables this to be done in real time without problem of artefacts[36]. Arterial phase lasts for about 30 s and venous phase for the next 90 s[37]. Pancreatic tumours are hypovascular with delayed contrast uptake and usually lack venous structure[13,38,39]. A time intensity curve can be generated using image software and the peak characteristics can give a clue to the underlying diagnosis. Results from most studies using CE EUS have been encouraging with sensitivity and specificity greater than 90%[13,14,38,40,41]. Seicean *et al*[38] measured the contrast uptake ratio index during CE EUS and found it to be significantly lower in pancreatic cancer than in mass forming chronic pancreatitis. A cut-off ratio of 0.17 had good discriminatory value[38]. The contrast enhancement and elastography techniques can also be used in combination. In a study using combination of above techniques, the positive predictive value was 96.7% in evaluating pseudotumour of chronic pancreatitis and pancreatic cancer[41]. The results of elastography, CE EUS and digital image analysis are encouraging but are affected by equipment characteristics and type of contrast used. Development of consensus guidelines and uniformity in performing these procedures will make it easier to integrate their use in clinical practice.

OTHER IMAGING MODALITIES

Computed tomography

Computed tomography (CT) was considered to be the gold standard for pancreatic parenchymal imaging. Conventional CT however has difficulty in differentiating between inflammatory and neoplastic masses as well as detecting lesions < 2 cm in diameter as small tumours are sometimes isoattenuated to background pancreatic parenchyma. Recent developments including 64 slice multidetector row CT (MDCT) have shown promise in evaluating pancreatic mass lesion[42,43]. During triple phase pancreatic protocol CT, normal pancreas shows early washout (first phase) while there is delayed washout in chronic pancreatitis[44]. On the other hand pancreatic cancer shows an increasing pattern without washout[44]. This can be quantitatively assessed using time attenuation curve and Yamada *et al*[44] have shown this technique to have 90.4% accuracy in differentiating pancreatic cancer from chronic pancreatitis. Lu *et al*[45] evaluated 15 patients with pancreatic pseudotumor and 64 patients with pancreatic cancer and quantitative hemodynamic information obtained using time density curve was useful in distinguishing the two conditions.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has traditionally been considered less sensitive than CT scan for assessing pancreatic mass lesions. T1 weighted images have similar features in both chronic pancreatitis and pancreatic cancer but T2 weighted images show different signal intensity pattern in inflammatory and neoplastic tissue[46]. Assessment of pancreatic ductal structures can sometimes provide a clue as pancreatic cancers may lack pancreatic ductal structures while a pseudotumour may contain dilated side branches[47]. Recent advances in techniques and technology have been effective in distinguishing between inflammatory and malignant mass of pancreas[42,43,48,49]: (1) Diffusion weighted MRI: Huang *et al*[50] studied 37 patients

Table 2 Data from other studies on role of endoscopic ultrasound in evaluating pancreatic mass lesions

Ref.	Study subjects	Procedure	Outcome[1]
Ardengh *et al*[12]	69 patients with pancreatic head mass	EUS	Sn-63.63% Sp-75.86%
		EUS FNA	Sn-72.7% Sp-100%
Das *et al*[16]	Normal-22 CP-12 PC-22	EUS, Digital image analysis	Sn-93% Sp-92%
Zhu *et al*[15]	CP-262 PC-126	EUS, Digital image analysis	Sn-96.25% Sp-93.38%
Hirsche *et al*[32]	70 patients with focal pancreatic lesion	EUS Elastography	Sn-41% Sp-53%
Giovannini *et al*[33]	121 patients with pancreatic mass lesion	EUS	Sn-92.3% Sp-68.9%
		EUS Elastography	Sn-92.3% Sp-80%
Iglesias-Garcia *et al*[35]	78 patients with malignant pancreatic tumour 42 patients with inflammatory pancreatic mass	EUS Elastography	Sn-100% Sp-85.5%
Iglesias-Garcia *et al*[30]	86 patients with pancreatic mass (27 of them had inflammatory mass)	Quantitative EUS Elastography	Sn-100% Sp-92.9%
Seicean *et al*[38]	30 patients with pancreatic lesion (12 had pseudotumour)	CE harmonic-EUS	Sn-80% Sp-91.7%
Saftoui *et al*[41]	Focal pancreatic mass lesion (21 had pseudotumour)	CE + elastography during EUS	Sn-75.85 Sp-95.2%
Saftoui *et al*[34]	258 patients with focal pancreatic mass	Quantitative EUS Elastography	Sn-93.4% Sp-66%
Hocke *et al*[14]	Focal CP-39	EUS	Sn-61.5% Sp-73.7%
		EUS elastography	Sn-33.4% Sp-94.7%
	PC-19	CELMI-EUS	Sn-76.9% Sp-84.2%
		CEHMI-EUS	Sn-89.5% Sp-84.2%
Gheona *et al*[40]	PC-32 Pseudotumoural pancreatitis-19	Quantitative CE-EUS	Sn-93.7% Sp-89.4%

[1]Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; CELMI: Contrast enhanced low mechanical index; CEHMI: Contrast enhanced high mechanical index; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

with pancreatic cancer and 14 patients with mass forming chronic pancreatitis using diffusion weighted MRI imaging with quantification techniques and showed that this technique can differentiate mass forming chronic pancreatitis from pancreatic cancer; (2) Gadolinium (Gd) enhanced 3D- Gradient echo: Kim *et al*[51] studied 22 patients with pancreatic mass (pancreatic cancer: 14; chronic pancreatitis: 8) using Gd enhanced 3D-GE and found that this technique differentiated pancreatic cancer from inflammatory mass with a sensitivity and specificity of 93% (13/14) and 75% (6/8), respectively; (3) Time signal intensity curve obtained during contrast enhanced MRI is another technique that helps in differentiating between malignant and inflammatory lesions[50]; and (4) Magnetic resonance spectroscopy: Focal pancreatitis has lower lipid content compared to cancer due to difference in fibrous tissue content in the two conditions. This can be detected by magnetic resonance spectroscopy and helps distinguish inflammatory mass from cancer[52].

Positron emission tomography

The sensitivity of FDG-positron emission tomography (PET) for differentiating pancreatic cancer from chronic pancreatitis is more than that of CT or MRI[53]. Singer and colleagues have shown that pancreatic cancer causes focal tracer enhancement while chronic pancreatitis causes diffuse enhancement[54]. This feature had 86.4% sensitivity and 78.9% specificity in distinguishing cancer from benign mass in their study on 41 patients. PET-CT detects unsuspected metastasis to liver, lung and bone which aids in discriminating between inflammatory mass and cancer. The sensitivity of PET is superior to CT in detecting lesions less than 2 cm in diameter, but CT scanning is superior to PET for diagnosing cancers larger than 4 cm in diameter because of lower metabolic rates in larger tumors[55].

Molecular techniques

Advances in molecular techniques and tools like microarray, nuclear magnetic resonance and mass

spectrometry have enabled detection of a large number of molecules rapidly. At cellular level genetic information gets transcribed into m RNA which gets translated into proteins and subsequently metabolised. Alteration of genes at cellular level in neoplastic cells leads to changes in protein and metabolites and this can be detected using "omics" technology[56-58]. Genomics aims at detecting genes, proteomics at detecting set of expressed proteins and metabolomics the metabolic profile. While molecular techniques can detect a large array of products, filtering out the specific markers useful for diagnosing different conditions remains a challenge. A proteomics based study from United States, aimed to identify the plasma protein profile in subjects with chronic pancreatitis, pancreatic cancer and non-pancreatic disease controls[59]. They identified more than 1300 proteins and found that a composite marker of TIMP1 and ICAM1 performed better than CA19-9 in differentiating pancreatic cancer from rest of the group. They also suggested that a protein called AZGP1 could serve as a biomarker for chronic pancreatitis[59]. Paulo *et al*[60] studied expressed proteins in chronic pancreatitis, pancreatic cancer and autoimmune pancreatitis and found a range of differentially expressed proteins in the three different groups. Using liquid chromatography with tandem mass spectrometry, they found that 29 proteins were exclusively expressed in chronic pancreatitis and 53 protein in pancreatic cancer[60]. These tests were conducted on tissue samples and hence can serve as an adjunct to histology but require validation in larger cohort.

Zhang *et al*[61] used NMR based metabolomics strategy to distinguish pancreatic cancer from chronic pancreatitis and healthy individuals and found the results promising. Patients with pancreatic cancer had a number of abnormalities in amino acid and lipid metabolism including elevated levels of N-acetyl glycoprotein and dimethylamine and reduced levels of citrate, alanine, glutamine. In another metabolomics based study done employing gas chromatography mass spectrometry on subjects with chronic pancreatitis, pancreatic cancer and healthy volunteers, Kobayashi and colleagues were able to develop a model which performed reasonably well in differentiating PC from CP. Other studies have shown, Ca 242, M2 pyruvate kinase, PBF-4, PNA binding glycoprotein, nTert, MMP-2, Synuclein-gamma, and neopterin to be useful biomarkers in differentiating pancreatic cancer from chronic pancreatitis[59,62,63]. A study from Germany has shown that micro RNA abundance measured in tissue and blood performs well in distinguishing chronic pancreatitis and pancreatic cancer[64]. Overall, molecular tools appear promising but are not yet ready for clinical application.

CONCLUSION

There have been a number of developments in imaging and molecular technologies to aid in differentiating benign from malignant mass lesion in patients with chronic pancreatitis. While some like EUS-FNA and advanced CT/MRI techniques are already in clinical use, technologies like CE EUS, EUS elastography and digital image analysis require development of standardised protocol, consensus and operator training facilities before they can be inducted into regular clinical usage. The molecular techniques are still in the early stage of development. Continued research and development is required to help in the correct diagnosis of this challenging condition.

REFERENCES

1 **McKay CJ**, Glen P, McMillan DC. Chronic inflammation and pancreatic cancer. *Best Pract Res Clin Gastroenterol* 2008; **22**: 65-73 [PMID: 18206813 DOI: 10.1016/j.bpg.2007.11.007]

2 **Raimondi S**, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010; **24**: 349-358 [PMID: 20510834 DOI: 10.1016/j.bpg.2010.02.007]

3 **Jimenez E**, Castillo CF. Tumors of Pancreas. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 9th ed. Philadelphia: Saunders Elsevier, 2010: 1017-1024

4 **Oto A**, Eltorky MA, Dave A, Ernst RD, Chen K, Rampy B, Chaljub G, Nealon W. Mimicks of pancreatic malignancy in patients with chronic pancreatitis: correlation of computed tomography imaging features with histopathologic findings. *Curr Probl Diagn Radiol* 2006; **35**: 199-205 [PMID: 16949476 DOI: 10.1067/j.cpradiol.2006.06.001]

5 **Bedi MM**, Gandhi MD, Jacob G, Lekha V, Venugopal A, Ramesh H. CA 19-9 to differentiate benign and malignant masses in chronic pancreatitis: is there any benefit? *Indian J Gastroenterol* 2009; **28**: 24-27 [PMID: 19529898 DOI: 10.1007/s12664-009-0005-4]

6 **Evans JD**, Morton DG, Neoptolemos JP. Chronic pancreatitis and pancreatic carcinoma. *Postgrad Med J* 1997; **73**: 543-548 [PMID: 9373592 DOI: 10.1136/pgmj.73.863.543]

7 **Perumal S**, Palaniappan R, Pillai SA, Velayutham V, Sathyanesan J. Predictors of malignancy in chronic calcific pancreatitis with head mass. *World J Gastrointest Surg* 2013; **5**: 97-103 [PMID: 23717745 DOI: 10.4240/wjgs.v5.i4.97]

8 **Taylor B**. Carcinoma of the head of the pancreas versus chronic pancreatitis: diagnostic dilemma with significant consequences. *World J Surg* 2003; **27**: 1249-1257 [PMID: 14502404 DOI: 10.1007/s00268-003-7245-8]

9 **Irisawa A**, Sato A, Sato M, Ikeda T, Suzuki R, Ohira H. Early diagnosis of small pancreatic cancer: role of endoscopic ultrasonography. *Dig Endosc* 2009; **21** Suppl 1: S92-S96 [PMID: 19691746 DOI: 10.1111/j.1443-1661.2009.00866.x]

10 **Gress FG**, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, Sherman S, Wiersema M, Lehman GA. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. *Gastrointest Endosc* 1999; **50**: 786-791 [PMID: 10570337 DOI: 10.1016/S0016-5107(99)70159-8]

11 **Sreenarasimhaiah J**. Efficacy of endoscopic ultrasound in characterizing mass lesions in chronic pancreatitis. *J Clin Gastroenterol* 2008; **42**: 81-85 [PMID: 18097295 DOI: 10.1097/MCG.0b013e31802c4bfb]

12 **Ardengh JC**, Lopes CV, Campos AD, Pereira de Lima LF, Venco F, Módena JL. Endoscopic ultrasound and fine needle aspiration in chronic pancreatitis: differential diagnosis between pseudotumoral masses and pancreatic cancer. *JOP* 2007; **8**: 413-421 [PMID: 17625292]

13 **Hocke M**, Schulze E, Gottschalk P, Topalidis T, Dietrich CF.

Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J Gastroenterol* 2006; **12**: 246-250 [PMID: 16482625]
14 **Hocke M**, Ignee A, Dietrich CF. Advanced endosonographic diagnostic tools for discrimination of focal chronic pancreatitis and pancreatic carcinoma--elastography, contrast enhanced high mechanical index (CEHMI) and low mechanical index (CELMI) endosonography in direct comparison. *Z Gastroenterol* 2012; **50**: 199-203 [PMID: 22298098 DOI: 10.1055/s-0031-1281824]
15 **Zhu M**, Xu C, Yu J, Wu Y, Li C, Zhang M, Jin Z, Li Z. Differentiation of pancreatic cancer and chronic pancreatitis using computer-aided diagnosis of endoscopic ultrasound (EUS) images: a diagnostic test. *PLoS One* 2013; **8**: e63820 [PMID: 23704940 DOI: 10.1371/journal.pone.0063820]
16 **Das A**, Nguyen CC, Li F, Li B. Digital image analysis of EUS images accurately differentiates pancreatic cancer from chronic pancreatitis and normal tissue. *Gastrointest Endosc* 2008; **67**: 861-867 [PMID: 18179797 DOI: 10.1016/j.gie.2007.08.036]
17 **Varadarajulu S**, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc* 2005; **62**: 728-736; quiz 751, 753 [PMID: 16246688]
18 **Iordache S**, Săftoiu A, Cazacu S, Gheonea DI, Dumitrescu D, Popescu C, Ciurea T. Endoscopic ultrasound approach of pancreatic cancer in chronic pancreatitis patients in a tertiary referral centre. *J Gastrointestin Liver Dis* 2008; **17**: 279-284 [PMID: 18836620]
19 **Fritscher-Ravens A**, Brand L, Knöfel WT, Bobrowski C, Topalidis T, Thonke F, de Werth A, Soehendra N. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. *Am J Gastroenterol* 2002; **97**: 2768-2775 [PMID: 12425546 DOI: 10.1111/j.1572-0241.2002.07020.x]
20 **Eloubeidi MA**, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. *J Gastroenterol Hepatol* 2008; **23**: 567-570 [PMID: 18397485 DOI: 10.1111/j.1440-1746.2007.05119.x]
21 **Khalid A**, Nodit L, Zahid M, Bauer K, Brody D, Finkelstein SD, McGrath KM. Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. *Am J Gastroenterol* 2006; **101**: 2493-2500 [PMID: 17029619 DOI: 10.1111/j.1572-0241.2006.00740.x]
22 **Salek C**, Benesova L, Zavoral M, Nosek V, Kasperova L, Ryska M, Strnad R, Traboulsi E, Minarik M. Evaluation of clinical relevance of examining K-ras, p16 and p53 mutations along with allelic losses at 9p and 18q in EUS-guided fine needle aspiration samples of patients with chronic pancreatitis and pancreatic cancer. *World J Gastroenterol* 2007; **13**: 3714-3720 [PMID: 17659731]
23 **Chen Y**, Zheng B, Robbins DH, Lewin DN, Mikhitarian K, Graham A, Rumpp L, Glenn T, Gillanders WE, Cole DJ, Lu X, Hoffman BJ, Mitas M. Accurate discrimination of pancreatic ductal adenocarcinoma and chronic pancreatitis using multimarker expression data and samples obtained by minimally invasive fine needle aspiration. *Int J Cancer* 2007; **120**: 1511-1517 [PMID: 17192896 DOI: 10.1002/ijc.22487]
24 **Bournet B**, Souque A, Senesse P, Assenat E, Barthet M, Lesavre N, Aubert A, O'Toole D, Hammel P, Levy P, Ruszniewski P, Bouisson M, Escourrou J, Cordelier P, Buscail L. Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with KRAS mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis. *Endoscopy* 2009; **41**: 552-557 [PMID: 19533561 DOI: 10.1055/s-0029-1214717]
25 **Takahashi K**, Yamao K, Okubo K, Sawaki A, Mizuno N, Ashida R, Koshikawa T, Ueyama Y, Kasugai K, Hase S, Kakumu S. Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA. *Gastrointest Endosc* 2005; **61**: 76-79 [PMID: 15672060 DOI: 10.1016/S0016-5107(04)02224-2]
26 **Seicean A**. Endoscopic ultrasound in chronic pancreatitis: where are we now? *World J Gastroenterol* 2010; **16**: 4253-4263 [PMID: 20818808 DOI: 10.3748/wjg.v16.i34.4253]
27 **Pei Q**, Zou X, Zhang X, Chen M, Guo Y, Luo H. Diagnostic value of EUS elastography in differentiation of benign and malignant solid pancreatic masses: a meta-analysis. *Pancreatology* 2012; **12**: 402-408 [PMID: 23127527 DOI: 10.1016/j.pan.2012.07.013]
28 **Iglesias-García J**, Lindkvist B, Lariño-Noia J, Domínguez-Muñoz JE. The role of EUS in relation to other imaging modalities in the differential diagnosis between mass forming chronic pancreatitis, autoimmune pancreatitis and ductal pancreatic adenocarcinoma. *Rev Esp Enferm Dig* 2012; **104**: 315-321 [PMID: 22738702 DOI: 10.4321/S1130-01082012000600006]
29 **Giovannini M**. Endoscopic ultrasound elastography. *Pancreatology* 2011; **11** Suppl 2: 34-39 [PMID: 21464585 DOI: 10.1159/000323496]
30 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; **139**: 1172-1180 [PMID: 20600020 DOI: 10.1053/j.gastro.2010.06.059]
31 **Janssen J**, Schlörer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. *Gastrointest Endosc* 2007; **65**: 971-978 [PMID: 17531630 DOI: 10.1016/j.gie.2006.12.057]
32 **Hirche TO**, Ignee A, Barreiros AP, Schreiber-Dietrich D, Jungblut S, Ott M, Hirche H, Dietrich CF. Indications and limitations of endoscopic ultrasound elastography for evaluation of focal pancreatic lesions. *Endoscopy* 2008; **40**: 910-917 [PMID: 19009483 DOI: 10.1055/s-2008-1077726]
33 **Giovannini M**, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Geneviève M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. *World J Gastroenterol* 2009; **15**: 1587-1593 [PMID: 19340900 DOI: 10.3748/wjg.15.1587]
34 **Săftoiu A**, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, Iglesias-Garcia J, Arcidiacono P, Will U, Giovannini M, Dietrich C, Havre R, Gheorghe C, McKay C, Gheonea DI, Ciurea T. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. *Endoscopy* 2011; **43**: 596-603 [PMID: 21437851 DOI: 10.1055/s-0030-1256314]
35 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. *Gastrointest Endosc* 2009; **70**: 1101-1108 [PMID: 19647248 DOI: 10.1016/j.gie.2009.05.011]
36 **Seicean A**, Badea R, Stan-Iuga R, Gulei I, Pop T, Pascu O. The added value of real-time harmonics contrast-enhanced endoscopic ultrasonography for the characterisation of pancreatic diseases in routine practice. *J Gastrointestin Liver Dis* 2010; **19**: 99-104 [PMID: 20361085]
37 **Claudon M**, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, Correas JM, Darge K, Dietrich C, D'Onofrio M, Evans DH, Filice C, Greiner L, Jäger K, Jong Nd, Leen E, Lencioni R, Lindsell D, Martegani A, Meairs S, Nolsøe C, Piscaglia F, Ricci P, Seidel G, Skjoldbye B, Solbiati L, Thorelius L, Tranquart F, Weskott HP, Whittingham T. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) - update 2008. *Ultraschall Med* 2008; **29**: 28-44 [PMID: 18270887 DOI: 10.1055/s-2007-963785]
38 **Seicean A**, Badea R, Stan-Iuga R, Mocan T, Gulei I, Pascu O. Quantitative contrast-enhanced harmonic endoscopic ultrasonography for the discrimination of solid pancreatic masses. *Ultraschall Med* 2010; **31**: 571-576 [PMID: 21080306 DOI: 10.1055/s-0029-1245833]
39 **Dietrich CF**, Ignee A, Braden B, Barreiros AP, Ott M, Hocke M. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. *Clin Gastroenterol Hepatol* 2008; **6**: 590-597.e1 [PMID: 18455699 DOI: 10.1016/j.cgh.2008.02.030]
40 **Gheonea DI**, Streba CT, Ciurea T, Săftoiu A. Quantitative low mechanical index contrast-enhanced endoscopic ultrasound for the differential diagnosis of chronic pseudotumoral pancreatitis

and pancreatic cancer. *BMC Gastroenterol* 2013; **13**: 2 [PMID: 23286918 DOI: 10.1186/1471-230X-13-2]
41 **Săftoiu A**, Iordache SA, Gheonea DI, Popescu C, Maloş A, Gorunescu F, Ciurea T, Iordache A, Popescu GL, Manea CT. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). *Gastrointest Endosc* 2010; **72**: 739-747 [PMID: 20674916 DOI: 10.1016/j.gie.2010.02.056]
42 **Chaudhary V**, Bano S. Imaging of the pancreas: Recent advances. *Indian J Endocrinol Metab* 2011; **15**: S25-S32 [PMID: 21847450 DOI: 10.4103/2230-8210.83060]
43 **Bipat S**, Phoa SS, van Delden OM, Bossuyt PM, Gouma DJ, Laméris JS, Stoker J. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. *J Comput Assist Tomogr* 2005; **29**: 438-445 [PMID: 16012297 DOI: 10.1097/01.rct.0000164513.23407.b3]
44 **Yamada Y**, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. *Abdom Imaging* 2010; **35**: 163-171 [PMID: 19771464 DOI: 10.1007/s00261-009-9579-7]
45 **Lu N**, Feng XY, Hao SJ, Liang ZH, Jin C, Qiang JW, Guo QY. 64-slice CT perfusion imaging of pancreatic adenocarcinoma and mass-forming chronic pancreatitis. *Acad Radiol* 2011; **18**: 81-88 [PMID: 20951612 DOI: 10.1016/j.acra.2010.07.012]
46 **Ragozzino A**, Scaglione M. Pancreatic head mass: what can be done? Diagnosis: magnetic resonance imaging. *JOP* 2000; **1**: 100-107 [PMID: 11854565]
47 **Schima W**. MRI of the pancreas: tumours and tumour-simulating processes. *Cancer Imaging* 2006; **6**: 199-203 [PMID: 17208676 DOI: 10.1102/1470-7330.2006.0035]
48 **Hakimé A**, Giraud M, Vullierme MP, Vilgrain V. [MR imaging of the pancreas]. *J Radiol* 2007; **88**: 11-25 [PMID: 17299363 DOI: 10.1016/S0221-0363(07)89785-X]
49 **Sandrasegaran K**, Lin C, Akisik FM, Tann M. State-of-the-art pancreatic MRI. *AJR Am J Roentgenol* 2010; **195**: 42-53 [PMID: 20566796 DOI: 10.2214/AJR.10.4421]
50 **Huang WC**, Sheng J, Chen SY, Lu JP. Differentiation between pancreatic carcinoma and mass-forming chronic pancreatitis: usefulness of high b value diffusion-weighted imaging. *J Dig Dis* 2011; **12**: 401-408 [PMID: 21955434 DOI: 10.1111/j.1751-2980.2011.00517.x]
51 **Kim JK**, Altun E, Elias J, Pamuklar E, Rivero H, Semelka RC. Focal pancreatic mass: distinction of pancreatic cancer from chronic pancreatitis using gadolinium-enhanced 3D-gradient-echo MRI. *J Magn Reson Imaging* 2007; **26**: 313-322 [PMID: 17610286 DOI: 10.1002/jmri.21010]
52 **Cho SG**, Lee DH, Lee KY, Ji H, Lee KH, Ros PR, Suh CH. Differentiation of chronic focal pancreatitis from pancreatic carcinoma by in vivo proton magnetic resonance spectroscopy. *J Comput Assist Tomogr* 2005; **29**: 163-169 [PMID: 15772531 DOI: 10.1097/01.rct.0000153956.33296.b5]
53 **Bares R**, Klever P, Hauptmann S, Hellwig D, Fass J, Cremerius U, Schumpelick V, Mittermayer C, Büll U. F-18 fluorodeoxyglucose PET in vivo evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. *Radiology* 1994; **192**: 79-86 [PMID: 8208970 DOI: 10.1148/radiology.192.1.8208970]
54 **Singer E**, Gschwantler M, Plattner D, Kriwanek S, Armbruster C, Schueller J, Feichtinger H, Roka R, Moeschl P, Weiss W, Kroiss A. Differential diagnosis of benign and malign pancreatic masses with 18F-fluordeoxyglucose-positron emission tomography recorded with a dual-head coincidence gamma camera. *Eur J Gastroenterol Hepatol* 2007; **19**: 471-478 [PMID: 17489057 DOI: 10.1097/MEG.0b013e328011741d]
55 **Delbeke D**, Rose DM, Chapman WC, Pinson CW, Wright JK, Beauchamp RD, Shyr Y, Leach SD. Optimal interpretation of FDG PET in the diagnosis, staging and management of pancreatic carcinoma. *J Nucl Med* 1999; **40**: 1784-1791 [PMID: 10565771]
56 **Thomas JK**, Kim MS, Balakrishnan L, Nanjappa V, Raju R, Marimuthu A, Radhakrishnan A, Muthusamy B, Khan AA, Sakamuri S, Tankala SG, Singal M, Nair B, Sirdeshmukh R, Chatterjee A, Prasad TS, Maitra A, Gowda H, Hruban RH, Pandey A. Pancreatic Cancer Database: an integrative resource for pancreatic cancer. *Cancer Biol Ther* 2014; **15**: 963-967 [PMID: 24839966 DOI: 10.4161/cbt.29188]
57 **Bramhall SR**. The use of molecular technology in the differentiation of pancreatic cancer and chronic pancreatitis. *Int J Pancreatol* 1998; **23**: 83-100 [PMID: 9629506]
58 **Fang F**, He X, Deng H, Chen Q, Lu J, Spraul M, Yu Y. Discrimination of metabolic profiles of pancreatic cancer from chronic pancreatitis by high-resolution magic angle spinning 1H nuclear magnetic resonance and principal components analysis. *Cancer Sci* 2007; **98**: 1678-1682 [PMID: 17727683 DOI: 10.1111/j.1349-7006.2007.00589.x]
59 **Pan S**, Chen R, Crispin DA, May D, Stevens T, McIntosh MW, Bronner MP, Ziogas A, Anton-Culver H, Brentnall TA. Protein alterations associated with pancreatic cancer and chronic pancreatitis found in human plasma using global quantitative proteomics profiling. *J Proteome Res* 2011; **10**: 2359-2376 [PMID: 21443201 DOI: 10.1021/pr101148r]
60 **Paulo JA**, Kadiyala V, Brizard S, Banks PA, Steen H, Conwell DL. A proteomic comparison of formalin-fixed paraffin-embedded pancreatic tissue from autoimmune pancreatitis, chronic pancreatitis, and pancreatic cancer. *JOP* 2013; **14**: 405-414 [PMID: 23846938]
61 **Zhang L**, Jin H, Guo X, Yang Z, Zhao L, Tang S, Mo P, Wu K, Nie Y, Pan Y, Fan D. Distinguishing pancreatic cancer from chronic pancreatitis and healthy individuals by (1)H nuclear magnetic resonance-based metabonomic profiles. *Clin Biochem* 2012; **45**: 1064-1069 [PMID: 22613268 DOI: 10.1016/j.clinbiochem.2012.05.012]
62 **Kobayashi T**, Nishiumi S, Ikeda A, Yoshie T, Sakai A, Matsubara A, Izumi Y, Tsumura H, Tsuda M, Nishisaki H, Hayashi N, Kawano S, Fujiwara Y, Minami H, Takenawa T, Azuma T, Yoshida M. A novel serum metabolomics-based diagnostic approach to pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 571-579 [PMID: 23542803 DOI: 10.1158/1055-9965.EPI-12-1033]
63 **Talar-Wojnarowska R**, Gasiorowska A, Olakowski M, Lekstan A, Lampe P, Malecka-Panas E. Clinical value of serum neopterin, tissue polypeptide-specific antigen and CA19-9 levels in differential diagnosis between pancreatic cancer and chronic pancreatitis. *Pancreatology* 2010; **10**: 689-694 [PMID: 21242708 DOI: 10.1159/000320693]
64 **Bauer AS**, Keller A, Costello E, Greenhalf W, Bier M, Borries A, Beier M, Neoptolemos J, Büchler M, Werner J, Giese N, Hoheisel JD. Diagnosis of pancreatic ductal adenocarcinoma and chronic pancreatitis by measurement of microRNA abundance in blood and tissue. *PLoS One* 2012; **7**: e34151 [PMID: 22511932 DOI: 10.1371/journal.pone.0034151]

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Collagenous gastritis: Review

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Abstract

Collagenous gastritis is a rare disease characterized by the subepithelial deposition of collagen bands thicker than 10 μm and the infiltration of inflammatory mononuclear cells in the lamina propria. Collagenous colitis and collagenous sprue have similar histological characteristics to collagenous gastritis and are thought to be part of the same disease entity. However, while collagenous colitis has become more common in the field of gastroenterology, presenting with clinical symptoms of chronic diarrhea in older patients, collagenous gastritis is rare. Since the disease was first reported in 1989, only 60 cases have been documented in the English literature. No safe and effective treatments have been identified from randomized, controlled trials. Therefore, better understanding of the disease and the reporting of more cases will help to establish diagnostic criteria and to develop therapeutic strategies. Therefore, here we review the clinical characteristics, endoscopic and histological findings, treatment, and clinical outcomes from case reports and case series published to date, and provide a summary of the latest information on the disease. This information will contribute to improved knowledge of collagenous gastritis so physicians can recognize and correctly diagnose the disease, and will help to develop a standard therapeutic strategy for future clinical trials.

Key words: Collagenous gastritis; Collagen deposition; Collagenous colitis; Nodularity

Core tip: The diagnosis of collagenous gastritis is based on the histological findings of collagen bands thicker than 10 μm in the subepithelial layer and infiltration of inflammatory mononuclear cells in the lamina propria. Similar histological changes are seen in the colon in collagenous colitis. While there are many cases of collagenous colitis published in the literature, there are only 60 reported cases of collagenous gastritis since the disease was first identified in 1989. The present review discusses the characteristics of this disease entity and summarizes the cases reported to date. Better knowledge and understanding of collagenous gastritis will help physicians to diagnose the disease, and the accumulation of future cases will help to develop a standard therapeutic strategy.

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INTRODUCTION

Collagenous gastroenteritides include collagenous gastritis, collagenous sprue, and collagenous colitis. This disease entity is relatively uncommon and believed to be rare. The diseases are characterized by marked subepithelial collagen deposition accompanying with mucosal inflammatory infiltrate[1-5]. The exact etiology and pathogenesis of this inflammatory disorder remains unclear and clinical presentations are related to the region of the gastrointestinal tract involved. While collagenous colitis is the most frequently found in this disease category[5,6], collagenous gastritis and collagenous sprue involving the proximal side of the gastrointestinal tract is rarer. Recently, it is reported that the overall annual incidence of collagenous colitis ranges from 1.1 to 5.2 cases per 100000 population and it is a relatively frequent cause of chronic diarrhea in elderly patients[7]. For collagenous gastritis, Colleti reported first case of 15-year-old girl who presented with recurrent abdominal pain and gastrointestinal bleeding in 1989[8]. On endoscopy, nodular changes were seen in the stomach. Subepithelial collagen deposits and inflammatory infiltration of the lamina propria were observed on histological examination. Despite treatment with histamine H2-receptor antagonists, sucralfate, and furazolidone, no clinical or pathological improvement was achieved[8]. Since 1989, only 60 cases of collagenous gastritis have been reported in the English literature[2-4,8-40]. Because of the small number of cases, no standard therapy has been established based on randomized, controlled clinical trials. However, based on case reports, two phenotypes of the disease (pediatric and adult) have been defined[21]. The presenting symptoms of the pediatric type are mainly upper gastrointestinal, including abdominal pain and anemia secondary to the stomach-specific inflammation and collagen deposition[10,21]. In contrast, the adult type is characterized by the simultaneous occurrence of collagenous colitis, which may be related to autoimmune processes and celiac disease[21]. The endoscopic findings of mucosal nodularity and the histological findings of inflammatory infiltration with thick collagen deposits are common in both adult and pediatric disease. However, the areas of the gastrointestinal tract involved are different, raising the possibility of a different etiology[1,3]. Because the pathophysiology of collagenous gastritis remains uncertain, no effective therapeutic strategies have been developed. Better knowledge and understanding of the disease will help physicians make a correct diagnosis at an early stage, and may help to establish rational treatment options. In this paper, we review the clinical and pathological characteristics of the 60 cases[2-4,8-40] reported to date.

LITERATURE ANALYSIS

A literature search was conducted using PubMed and Ovid, with the term "collagenous gastritis." The literatures written in English from relevant publications were selected. We summarized the available information on demographics, clinical symptoms, endoscopic and histological findings, treatment, and the clinical course.

CLINICAL CHARACTERS

Among the 60 reported cases of collagenous gastritis, there was a slight female predominance (35 females, 25 males). The ages ranged from 9 mo to 80 years[2-4,8-40].

Clinical symptoms included abdominal pain in 26 cases[3,4,8-10,12-15,17,18,20,26,30-33,38-40], anemia in 24[2,4,8,10,11,14,16,17,19,21,22,30,36,37,39,40], diarrhea in 18[13,17,21-29,35-37], nausea and vomiting in 7[3,15,17,31,32], body weight loss in 4[3,23,35], abdominal distention in 3[24,32,36], gastrointestinal bleeding in 3[8,17,36], and fatigue[4], retrosternal pain[11], dyspepsia[2], perforated ulcer[17], dysphagia[17], and constipation[38] in 1 case each. Lagorce-Pages *et al*[21] reported that clinical symptoms differ between pediatric and adult patients based on the severity of the disease and part of the gastrointestinal tract involved. Pediatric patients typically present in their early teens with anemia and abdominal pain related to involvement of the stomach[3,21,33,38]. The adult type is characterized by more diffuse involvement of the gastrointestinal tract and typically presents with a chronic watery diarrhea associated with collagenous colitis and collagenous sprue[36,37]. Adult collagenous gastritis is also associated with autoimmune diseases, such as Sjögren syndrome[36], lymphocytic gastritis, lymphocytic colitis, and ulcerative colitis[37]. Of the 11 patients who presented with abdominal pain and anemia, 8 were teenagers (72%)[4,8,10,14,17,30]. Of the 18 patients who presented with diarrhea, 15 were older than 20 years (83%)[17,21-27,35-37] (Table 1). Ten of the adult patients had collagenous duodenitis, which is extremely rare, and of these, 9 also had collagenous colitis[2,40]. Our literature search revealed no difference in the presence of *Helicobacter pylori* infection between pediatric (n = 6)[15,19,28,29] and adult patients (n = 4)[9,21,33]. The eradication of *H. pylori* did not produce any therapeutic benefit. The clinical characteristics of the 60 published cases supported the differences between pediatric-type and adult-type collagenous gastritis reported to date. In the pediatric form of the disease, inflammation is limited to the stomach and patients present with relatively severe upper gastrointestinal symptoms. The adult form of collagenous gastritis often involves other parts of the gastrointestinal tract, and might be the part the collagenous gastroenteritides disease entity. In

Table 1 Summary of 60 collagenous gastritis patients

Ref.	Age (yr)	Gender	Symptoms					Endoscopic Findings				*H. pylori*	Collagen band (μm)		Treatment	Follow-up biopsy duration (yr)	Histological changes	Clinical course
			Abdominal pain	Anemia	Diarrhea	Nausea, vomiting	Others	Nodularity	Erythema	Erosion, gastritis	Others		Stomach	Colon				
[10]	7	F	+	+	-	-	-	-	-	+	-	NA	Yes	None	Oral iron supplementation, Proton-pump inhibitor	0.5	Improvement of inflammation remaining of collagen band	Improve
[11]	9	F	-	+	-	-	Retrosternal pain	-	+	-	-	-	13-96	< 5	Proton-pump inhibitor, Sucralfate, Steroid	1.1	No reduction	No change
[12]	9	F	+	-	-	-	-	-	-	+	-	-	35	None	Oral iron supplementation	4	Decrease of chronic gastritis, Unchanged collagen bands	Clinical remission
[13]	9	F	+	-	-	-	-	+	-	-	-	-	Yes	Yes	Oral iron supplementation	NA	NA	Improve
[14]	9	F	+	+	-	-	-	-	-	-	NA	NA	Yes	NA	Mesalazine		NA	Remain
[15]	12	F	-	-	-	+	-	+	-	-	-	+	NA	None	Proton-pump inhibitor	1	Severe erosive gastritis	Remain
[15]	12	F	+	-	-	-	-	+	-	-	-	+	NA	None	Proton-pump inhibitor	6	Decrease of nodules	Improve
[15]	12	F	+	-	-	-	-	+	-	-	-	+	NA	NA	Proton-pump inhibitor	0.17	NA	Improve
[16]	12	F	-	+	-	-	-	+	-	-	-	-	Yes	None	Oral iron supplementation	NA		
[17]	13	F	-	+	-	-	-	+	-	-	-	-	76	NA	None	NA	NA	NA
[18]	14	F	+	-	-	-	-	+	-	-	-	-	75	None	Proton-pump inhibitor, Sucralfate, H2-receptor antagonist	12	Gradual progression	Remain
[17]	14	F	-	-	-	+	-	-	-	+	-	-	23	NA	Proton-pump inhibitor	NA	NA	Remain
[8]	15	F	+	+	-	-	Gastrointestinal bleeding	+	-	-	-	-	75	None	H2-receptor antagonist, sucralfate, furazolidone	2	No reduction	NA
[19]	15	F	-	+	-	-	-	+	-	-	-	+	NA	NA	Proton-pump inhibitors, Oral iron supplementation, Steroid	0.83	NA	Clinical remission
[17]	15	F	+	+	-	-	-	+	-	-	-	-	69	None	Steroid	3.4	Decrease of inflammation	Improve
[4]	16	F	+	+	-	-	-	+	-	-	-	-	NA	None	H2-receptor antagonist, Proton-pump inhibitor, Oral iron supplementation,	6	No reduction	Improvement of anemia

[20]	20	F	+	-	-	-	-	+	-	-	-	-	30-70	None	Proton-pump inhibitor	2	No change	NA
[21]	22	F	-	+	-	-	-	+	-	-	-	-	40-45	NA	None	NA	NA	NA
[40]	22	F	+	+	-	-	Gastrointestinal bleeding	+	-	+	Duodenitis	-	60-100	None	H2-receptor antagonist, Proton-pump inhibitor	1	No change	Improve
[22]	25	F	-	+	-	-	-	+	-	-	-	-	24	Yes	None	0.25	No change	NA
[23]	25	F	-	-	+	-	-	-	-	-	NA	NA	Yes	NA	None	NA	NA	NA
[23]	25	F	-	-	+	-	Body weight loss	-	-	-	NA	NA	Yes	Yes	NA	NA	NA	NA
[39]	25	F	+	+	-	-	-	+	-	-	NA	-	17	None	H2-receptor antagonist, Proton-pump inhibitor	4	No change	No change
[24]	35	F	-	-	+	-	Abdominal distention	+	-	-	-	-	20-30	None	Sulfasalazine	NA	NA	Remission of diarrhea
[4]	39	F	-	+	-	-	Fatigue	-	-	-	Normal	-	NA	Yes	Gluten-free diet	4	No reduction	Improve
[21]	40	F	-	-	+	-	-	-	-	-	Normal	-	40-41	None	Steroid, Sulfasalazine, Parenteral nutrition	2	Resolve of collagen band	NA
[21]	52	F	-	+	-	-	-	-	-	-	Normal	+	15-20	None	None	NA	NA	NA
[17]	52	F	+	-	+	-	-	-	-	+	-	-	78	None	Gluten-free diet	NA	NA	Improve
[25]	57	F	-	-	+	-	-	-	+	-	-	-	20-40	> 30	Steroid	1.5	No change	Responded to steroid
[17]	57	F	+	-	-	-	-	+	-	-	-	-	40	NA	Gluten-free diet	NA	NA	Improve
[22]	58	F	-	-	+	-	-	+	-	-	-	-	15.8	None	Steroid	1.5	Improvement of inflammation remaining of collagen band	NA
[17]	62	F	-	-	-	+	-	-	-	+	-	-	94	NA	None	NA	NA	NA
[2]	68	F	-	+	-	-	Dyspepsia	+	-	-	-	-	None	None	Oral iron supplementation, Proton-pump inhibitor	0.83	Improvement of inflammation increase of collagen band	Partial relief
[26]	74	F	+	-	+	-	-	-	+	-	-	-	Yes	Yes	Proton-pump inhibitor	0.08	No change	Improve
[27]	75	F	-	-	+	-	-	-	-	-	Normal	NA	30-60	10-30	NA	NA	NA	NA
[28]	0.75	M	-	-	+	-	-	-	-	+	-	+	50	17	Steroid, Total parenteral nutrition	14	Gradual progression	Improve with total parenteral nutrition
[29]	2	M	-	-	+	-	-	-	-	+	-	+	> 5	NA	Proton-pump inhibitors, Mesalazine, Steroid, Bismuth subsalicylate	NA	NA	Improve
[30]	9	M	+	+	-	-	-	+	-	-	-	-	30-150	None	Oral iron supplementation	2	NA	NA
[21]	11	M	-	+	-	-	-	+	-	-	-	-	50-69	None	None	8	Moderate decrease	NA

[10]	11	M	+	+	-	-	-	+	-	-	-	NA	> 10	NA	Proton-pump inhibitor, Oral iron supplementation	5	Improvement of inflammation resolve of collagen band	Improve
[13]	15	M	-	-	+	-	-	+	-	-	-	-	30	30	Proton-pump inhibitor, Steroid, Mesalazine	NA	NA	Clinical remission
[17]	19	M	+	+	-	-	Perforation of ulcer	+	-	-	-	-	40	NA	Sucralfate	0.25	Improvement of inflammation decrease of collagen band	Improve
[38]	19	M	+	-	-	-	Constipation	+	-	-	-	NA	15	None	None	0.5	Progression	Improve
[31]	20	M	+	-	-	+	-	+	-	-	-	-	15-43	20-30	H2-receptor antagonist, Oral iron supplementation	4	Progression	No change
[32]	25	M	+	-	-	+	Abdominal distention	+	-	-	-	-	> 10	None	Proton-pump inhibitor	NA	NA	Improve
[33]	25	M	+	-	-	-	-	-	-	-	Normal	+	Yes	NA	None	NA	NA	NA
[17]	34	M	+	+	-	-	Gastrointestinal bleeding	+	-	-	-	-	78	NA	None	9.9	Gradual progression	NA
[33]	35	M	-	-	-	-	-	+	-	-	-	-	50	None	None	14	Increase	Increase
[21]	36	M	NA	NA	NA	NA	NA	-	-	-	NA	-	15-20	NA	None	NA	NA	NA
[35]	37	M	-	-	+	-	Body weight loss	+	-	-	-	-	120	None	Steroid, Azathioprine, Parenteral nutrition	1.67	No change	Improve
[36]	42	M	-	+	+	-	Abdominal distention, Rectal bleeding	-	+	-	-	NA	26-10	None	Gluten-free diet	0.25	No change	Improve
[9]	47	M	+	-	-	-	-	-	-	-	Normal	+	70	None	Proton-pump inhibitor	NA	NA	Improve
[17]	56	M	-	-	-	+	-	+	-	-	-	-	87	None	Steroid, Gluten-free diet	NA	NA	Improve
[3]	56	M	+	-	-	+	Body weight loss	-	-	+	-	NA	Yes	NA	NA	NA	NA	NA
[37]	57	M	-	+	+	-	-	-	+	-	-	NA	13-45	None	Steroid, Mesalazine	NA	NA	Improve
[17]	59	M	-	-	-	-	Dysphagia	-	-	-	Normal	-	54	NA	None	NA	NA	NA
[17]	68	M	-	-	+	-	-	-	-	+	-	-	20	NA	Steroid, Gluten-free diet	0.75	Gradual progression	Remain
[23]	72	M	-	-	+	-	Body weight loss	-	-	-	NA	NA	Yes	Yes	Steroid	NA	NA	Improve
[21]	77	M	-	-	-	-	-	-	-	+	-	+	20-28	NA	None	NA	NA	NA
[17]	80	M	-	+	+	-	-	+	-	-	-	-	47	None	Steroid	NA	NA	NA

NA: Not available.

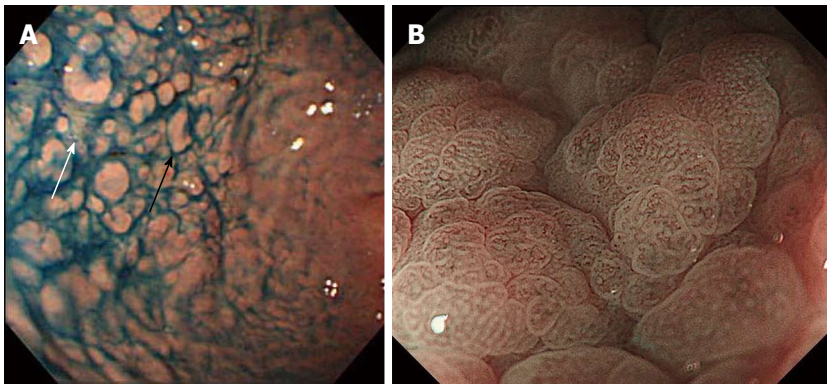

Figure 1 Endoscopic findings of collagenous gastritis. A: Nodular lesions (black arrow) in the greater curvature of the gastric body. Depressive mucosal lesions are seen in between nodular lesions (white arrow)[34]; B: Magnifying endoscopic image with narrow band imaging. Amorphous or absent surface pit pattern and abnormal capillary vessel patterns are seen in the depressed mucosal area[41].

adults, the presenting symptoms vary depending on the severity of the inflammation and the areas of the gastrointestinal tract involved.

ENDOSCOPIC FINDINGS

Nodularity of the gastric corpus is the characteristic endoscopic finding in collagenous gastritis. However, it is not seen in all cases. Our literature review found that 32 of the 60 patients showed endoscopic nodularity, with no difference in frequency between pediatric (n = 17)[4,8,10,13,15-19,21,29,30,38] and adult (n = 16)[2,17,20-22,24,31,32,34,35,39,40] cases (Table 1). The other endoscopic findings included mucosal erythema, erosions, and exudates. Normal gastric mucosa was found in 7 patients. The mucosal nodules were irregular in size and were located diffusely throughout the gastric body and antrum. The size and number depended on the severity of the inflammation (Figure 1A)[34]. Interestingly, in collagenous gastritis, it is not the mucosal thickening that causes the typical nodular appearance, but the depressed mucosa surrounding the nodules. This suggests that uneven inflammation causes glandular atrophy and collagen deposition in the depressed mucosa. Therefore, the nodular lesions show fewer inflammatory infiltrates and atrophic changes. In contrast, collagenous colitis shows a relatively even distribution of inflammation and atrophic changes, resulting in the homogeneous mucosal changes seen on the endoscopy of the colon. These findings have been supported by the recent results of narrow band imaging (NBI) studies and histological analysis. Kobayashi *et al*[41] used NBI with magnifying colonoscopy to examine the gastric mucosa in collagenous gastritis patients. The mucosal surface of the nodular lesions showed no marked changes and no abnormal capillary vessels were observed. However, as expected, the depressed mucosa surrounding these nodules showed an amorphous or absent surface structure and abnormal capillary vessels, including blind endings and irregular caliber changes (Figure 1B). This indicates that the depressed mucosal pattern is the result of inflammation with atrophic changes and collagen deposition, whereas the nodular lesions are the remaining undamaged mucosa[34].

PATHOLOGICAL FINDINGS

The pathological findings of collagenous gastritis are characterized by the infiltration of chronic inflammatory cells in the subepithelial layer, especially in the lamina propria, and the deposition of collagen bands thicker than 10 μm[13,37]. The inflammatory cells include lymphocytes, plasma cells, and eosinophils. Inflammation causes atrophic changes in the mucosal glands and leads to the depressed mucosal pattern found on endoscopy (Figure 2A)[34]. The pathological changes are less marked in the nodular mucosal lesions (Figure 2B)[34]. Therefore, a heterogeneous inflammatory pattern causes the nodular lesions in the stomach. These pathological findings suggest that several mucosal biopsies are needed for correct diagnosis, and careful mapping is required for the follow-up of mucosal inflammation and the thickness of collagen deposits. Our review found that most of the cases with information on the thickness of collagen deposits had bands thicker than 10 μm, with a range between 10 and 100 μm[11,20,30,40]. This supports the evidence for the heterogeneity of collagen deposition. The thickness of the collagen deposits may increase with disease duration; however, it may also be influenced by the location of the biopsy rather than the severity of the disease[16,17,19,21,37]. Total of 11[4,11,13,22,23,25-28] patients showed collagen deposition in colon and 7 (63%)[4,22,23,25-27] were older than 20 years old. These adult patients with coexisting collagenous colitis, showed diffuse and continuous collagen deposits in the colon but heterogeneous changes in the stomach[4]. This finding supports the hypothesis that the adult type of collagenous gastritis is part of the collagenous gastroenteritides, which tend to present with more severe symptoms related to involvement of the colon[4]. In addition, as 4 patients among 11 who showed collagenous colitis were young patients

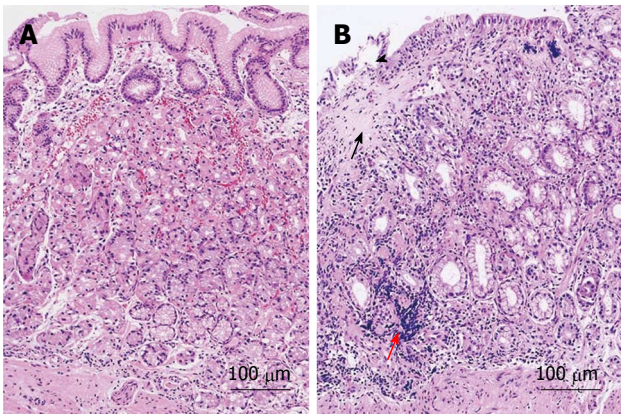

Figure 2 Histological findings of collagenous gastritis. A: Nodular mucosal lesion did not show marked inflammatory infiltration and collagen deposition; B: Depressive mucosal lesion showed a thick collagen deposition (black arrow) and inflammatory infiltrates (red arrow). The glandular atrophy and epithelial damage is marked (black arrowhead)[34].

(36%)[11,13,28], it is suggested that the disease type might not only be related to the age, but the etiology reflecting the tract involved.

Collagen deposition can be clearly visualized with Masson Trichrome staining. Collagen samples have been typed in a few patients[4,18,20,21,25], with types Ⅲ and Ⅵ identified. Some samples were positive for tenascin, a marker of cell proliferation and migration[4,42]. Type Ⅲ collagen is released from subepithelial fibroblasts to repair damage caused by inflammation. Therefore, the collagen synthesis in collagenous gastritis is not a primary pathology but a reparative response[4]. The study focusing on the collagen tissue type may contribute to clarify the etiology and help to differentially diagnose adult and pediatric types. The pathological findings reported in the published cases support the evidence that the endoscopic finding of nodularity is the result of heterogeneous inflammation and the destruction of mucosal glands and the surrounding mucosa (Table 2). However, the reason for the uneven inflammation in the stomach, in contrast to the relatively homogeneous inflammation in the colon, remains unclear.

THERAPY

Because of the small number of patients and the unknown etiology, there is no established standard therapy for collagenous gastritis. Anti-secretary agents including proton-pump inhibitors[2,4,9-11,13,15,17-20,26,29,32,39,40], and H2-receptor antagonists[4,8,18,39,40], steroids[11,13,17,19,21-23,25,28,29,35,37], iron supplementation[2,4,10,12,13,16,19,30], and hypoallergenic diets[4,17,36] have been tried with limited success (Table 1). Other treatment modalities, such as sucralfate[8,11,17,18], mesalazine[13,14,29,37], bismuth subsalicylate[29], furazolidone[8], sulfasalazine[21,24], azathioprine[35], and parenteral nutrition[21,28,35] have also been tested. A few patients have shown improvement of the clinical symptoms but no randomized, controlled trials have been performed. Further cases are needed to establish a standard therapeutic strategy. However, potential therapeutic approaches are complicated by the possibility that the pediatric and adult forms of the disease may have different etiologies. Furthermore, it remains unclear whether the pediatric type transforms to the adult type over time.

Table 2 Difference of mucosal pattern

Nodular mucosa	Depressive mucosa
No significant inflammation	Infiltration of inflammatory cells
Irregular distribution	Atrophic glands
Irregular size	Collagen band
Normal mucosal surface pattern	Amorphous or absent surface structure
	Abnormal capillary vessels

FOLLOW UP

The course and prognosis of collagenous gastritis remain unclear. The case reports include 30 patients who had undergone follow-up (Table 1). The median follow-up period was 2 years (0.08-14) and the clinical course and the response to therapy was evaluated. Kamimura *et al*[34] reported that in a patient followed for 14 years, the nodular appearance on endoscopy became more conspicuous and extended throughout the stomach. Histology showed that the thickness of collagen deposits increased over the 14 years. As discussed above, the heterogeneity of inflammation affects the thickness of the collagen deposits. Therefore, it is difficult to conclude that the collagen bands did become thicker. However, Billiemaz *et al*[28] reported similar endoscopic and histological findings of gradual disease progression during long-term follow-up. Conversely, Winslow *et al*[18] found no changes in the nodular appearance on endoscopy during the 12 year follow-up of one patient. Over the same 12 year period, biopsies showed patchy, chronic active gastritis with gradual progression in disease severity, although the collagen deposits did not appear to become more diffusely distributed or thicker over time. Lagorce-Pages *et al*[21] reported on 2 patients who showed complete absence of collagen deposits (40-year-old female) or a moderate decrease (11-year-old male) in the thickness of subepithelial collagen deposits on biopsy obtained 2 and 8 years after the initial diagnosis, respectively. The patient who recovered had been treated with steroid, salazopyrin, and parenteral alimentation. Hijaz *et al*[10] also reported on a patient who showed improvement of inflammation and an absence of collagen deposits 5 years after the initial diagnosis. This patient was treated with oral iron supplementation and proton-pump inhibitors[10]. Leung *et al*[17] reported a case of a 19-year-old male

Table 3 Differences of adult and pediatric type of collagenous gastritis

	Pediatric type	Adult type
Etiology	Unknown	Systematic disease, Autoimmune disease, drug induced
Gastrointestinal tract involved	Stomach	Stomach, colon, duodenum
Symptoms	Abdominal pain, anemia	Diarrhea
Endoscopy	Heterogeneous, Nodular pattern,	Homogeneous
Histology	Heterogeneous inflammatory infiltration, collagen band	Homogeneous inflammation

who showed improvement of inflammation and a decrease in the thickness of collagen deposits 3 mo after treatment with sucralfate[17]. On the other hand, Vakiani *et al*[22] and Rustagi *et al*[2] reported on patients who showed improvement of inflammation but unchanged or thicker collagen deposits after treatment with steroids and budesonide for 1.5 years, and oral iron supplementation and a proton-pump inhibitor for 0.83 years. These reports suggest that the inflammation can be managed by treatment. However, in most cases, the collagen deposits remain unchanged or become thicker as a result of continued inflammation. There was no evidence of the transformation of the pediatric-type disease to adult-type among the case reports.

DISCUSSION

Collagenous gastritis is a rare clinicopathological entity with only 60 cases reported to date[2-4,8-40] (Table 1). Although a primary vascular abnormality causing increased vascular permeability and collagen deposition has been proposed, the etiology of the disease is poorly understood[10]. The symptoms vary depending on the area of gastrointestinal tract involved, and in young patients, abdominal pain and anemia occur secondary to stomach-specific infiltration. Multiple areas are involved in adult patients, who often show chronic diarrhea because of coexisting collagenous colitis[3,5,6,21]. Characteristic differences are summarized in Table 3 and our review supports this hypothesis. Of the 11 patients who presented with abdominal pain and anemia, 8 were teenagers (72%)[4,8,10,14,17,30]. Conversely, of the 18 patients who presented with diarrhea, 83% (15 patients) were adults[17,21-27,35-37]. This suggests that adult-type collagenous gastritis is part of the collagenous gastroenteritides disease entity. The endoscopic findings include relative nodular changes in the mucosa, due to the chronic inflammatory infiltration, mucosal atrophy, and the deposition of bands of collagen. Compared with the diffuse and continuous deposition seen in collagenous colitis, the changes in collagenous gastritis are heterogeneous. The reason for this heterogeneity remains unclear, but it might be related to the etiology of gastritis. In addition, as 4 among 11 patients who had collagenous colitis were young patients[11,13,28], it is suggested that the disease type might not only be related to the age, but the etiology reflecting the tract involved.

Compared with collagenous gastritis, more patients are diagnosed with collagenous colitis. In these patients, adult-type collagenous gastritis may coexist. Therefore, upper endoscopy is recommended. In addition, multiple mucosal biopsies are needed because of the heterogeneous inflammatory pattern. Some areas of the stomach may show normal mucosa and our review identified 7 patients with endoscopically normal mucosa. Currently, transition from pediatric-type to adult-type disease is thought to be rare. However, more cases are needed to better understand this disease entity and to establish a standard therapeutic strategy.

REFERENCES

1 **Nielsen OH**, Riis LB, Danese S, Bojesen RD, Soendergaard C. Proximal collagenous gastroenteritides: clinical management. A systematic review. *Ann Med* 2014; **46**: 311-317 [PMID: 24716737 DOI: 10.3109/07853890.2014.899102]

2 **Rustagi T**, Rai M, Scholes JV. Collagenous gastroduodenitis. *J Clin Gastroenterol* 2011; **45**: 794-799 [PMID: 21346601 DOI: 10.1097/MCG.0b013e31820c6018]

3 **Gopal P**, McKenna BJ. The collagenous gastroenteritides: similarities and differences. *Arch Pathol Lab Med* 2010; **134**: 1485-1489 [PMID: 20923305 DOI: 10.1043/2010-0295-CR.1]

4 **Brain O**, Rajaguru C, Warren B, Booth J, Travis S. Collagenous gastritis: reports and systematic review. *Eur J Gastroenterol Hepatol* 2009; **21**: 1419-1424 [PMID: 19730387 DOI: 10.1097/MEG.0b013e32832770fa]

5 **Freeman HJ**. Complications of collagenous colitis. *World J Gastroenterol* 2008; **14**: 1643-1645 [PMID: 18350593 DOI: 10.3748/wjg.14.1643]

6 **Camarero C**, Leon F, Colino E, Redondo C, Alonso M, Gonzalez C, Roy G. Collagenous colitis in children: clinicopathologic, microbiologic, and immunologic features. *J Pediatr Gastroenterol Nutr* 2003; **37**: 508-513 [PMID: 14508225 DOI: 10.1097/00005176-200310000-00020]

7 **Williams JJ**, Beck PL, Andrews CN, Hogan DB, Storr MA. Microscopic colitis -- a common cause of diarrhoea in older adults. *Age Ageing* 2010; **39**: 162-168 [PMID: 20065357]

8 **Colletti RB**, Trainer TD. Collagenous gastritis. *Gastroenterology* 1989; **97**: 1552-1555 [PMID: 2583419]

9 **Al-Kandari A**, Al-Alardati H, Sayadi H, Al-Judaibi B, Mawardi M. An unusual case of collagenous gastritis in a middle- aged woman with systemic lupus erythromatosis: a case report. *J Med Case Rep* 2014; **8**: 278 [PMID: 25135519 DOI: 10.1186/1752-1947-8-278]

10 **Hijaz NM**, Septer SS, Degaetano J, Attard TM. Clinical outcome of pediatric collagenous gastritis: case series and review of literature. *World J Gastroenterol* 2013; **19**: 1478-1484 [PMID: 23538318 DOI: 10.3748/wjg.v19.i9.1478]

11 **Côté JF**, Hankard GF, Faure C, Mougenot JF, Holvoet L, Cézard JP, Navarro J, Peuchmaur M. Collagenous gastritis revealed by severe anemia in a child. *Hum Pathol* 1998; **29**: 883-886 [PMID: 9712433]

12 **Ravikumara M**, Ramani P, Spray CH. Collagenous gastritis: a case report and review. *Eur J Pediatr* 2007; **166**: 769-773 [PMID: 17453238 DOI: 10.1007/s00431-007-0450-y]
13 **Suskind D**, Wahbeh G, Murray K, Christie D, Kapur RP. Collagenous gastritis, a new spectrum of disease in pediatric patients: two case reports. *Cases J* 2009; **2**: 7511 [PMID: 19829984 DOI: 10.4076/1757-1626-2-7511]
14 **Camarero Salces C**, Enes Romero P, Redondo C, Rizo Pascual JM, Roy Ariño G. Collagenous colitis and collagenous gastritis in a 9 year old girl: a case report and review of the literature. *Acta Gastroenterol Belg* 2011; **74**: 468-474 [PMID: 22103057]
15 **Kori M**, Cohen S, Levine A, Givony S, Sokolovskaia-Ziv N, Melzer E, Granot E. Collagenous gastritis: a rare cause of abdominal pain and iron-deficiency anemia. *J Pediatr Gastroenterol Nutr* 2007; **45**: 603-606 [PMID: 18030241 DOI: 10.1097/MPG.0b013e31803cd545]
16 **Wilson C**, Thompson K, Hunter C. Nodular collagenous gastritis. *J Pediatr Gastroenterol Nutr* 2009; **49**: 157 [PMID: 19561541 DOI: 10.1097/MPG.0b013e3181ab6a43]
17 **Leung ST**, Chandan VS, Murray JA, Wu TT. Collagenous gastritis: histopathologic features and association with other gastrointestinal diseases. *Am J Surg Pathol* 2009; **33**: 788-798 [PMID: 19295410 DOI: 10.1097/PAS.0b013e318196a67f]
18 **Winslow JL**, Trainer TD, Colletti RB. Collagenous gastritis: a long-term follow-up with the development of endocrine cell hyperplasia, intestinal metaplasia, and epithelial changes indeterminate for dysplasia. *Am J Clin Pathol* 2001; **116**: 753-758 [PMID: 11710694 DOI: 10.1309/3WM2-THU3-3Q2A-DP47]
19 **Dray X**, Reignier S, Vahedi K, Lavergne-Slove A, Marteau P. Collagenous gastritis. *Endoscopy* 2007; **39** Suppl 1: E292-E293 [PMID: 17957644 DOI: 10.1055/s-2007-966730]
20 **Kajino Y**, Kushima R, Koyama S, Fujiyama Y, Okabe H. Collagenous gastritis in a young Japanese woman. *Pathol Int* 2003; **53**: 174-178 [PMID: 12608899 DOI: 10.1046/j.1440-1827.2003.01451.x]
21 **Lagorce-Pages C**, Fabiani B, Bouvier R, Scoazec JY, Durand L, Flejou JF. Collagenous gastritis: a report of six cases. *Am J Surg Pathol* 2001; **25**: 1174-1179 [PMID: 11688577 DOI: 10.1097/00000478-200109000-00008]
22 **Vakiani E**, Arguelles-Grande C, Mansukhani MM, Lewis SK, Rotterdam H, Green PH, Bhagat G. Collagenous sprue is not always associated with dismal outcomes: a clinicopathological study of 19 patients. *Mod Pathol* 2010; **23**: 12-26 [PMID: 19855376 DOI: 10.1038/modpathol.2009.151]
23 **Maguire AA**, Greenson JK, Lauwers GY, Ginsburg RE, Williams GT, Brown IS, Riddell RH, O'Donoghue D, Sheahan KD. Collagenous sprue: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 2009; **33**: 1440-1449 [PMID: 19641452 DOI: 10.1097/PAS.0b013e3181ae2545]
24 **Groisman GM**, Meyers S, Harpaz N. Collagenous gastritis associated with lymphocytic colitis. *J Clin Gastroenterol* 1996; **22**: 134-137 [PMID: 8742654 DOI: 10.1097/00004836-199603000-00013]
25 **Castellano VM**, Muñoz MT, Colina F, Nevado M, Casis B, Solís-Herruzo JA. Collagenous gastrobulbitis and collagenous colitis. Case report and review of the literature. *Scand J Gastroenterol* 1999; **34**: 632-638 [PMID: 10440616 DOI: 10.1080/00365529750026128]
26 **Freeman HJ**. Topographic mapping of collagenous gastritis. *Can J Gastroenterol* 2001; **15**: 475-478 [PMID: 11493952]
27 **Stolte M**, Ritter M, Borchard F, Koch-Scherrer G. Collagenous gastroduodenitis on collagenous colitis. *Endoscopy* 1990; **22**: 186-187 [PMID: 2209504 DOI: 10.1055/s-2007-1012837]
28 **Billiémaz K**, Robles-Medranda C, Le Gall C, Gay C, Mory O, Clémenson A, Bouvier R, Teyssier G, Lachaux A. A first report of collagenous gastritis, sprue, and colitis in a 9-month-old infant: 14 years of clinical, endoscopic, and histologic follow-up. *Endoscopy* 2009; **41** Suppl 2: E233-E234 [PMID: 19757370 DOI: 10.1055/s-2008-1077440]
29 **Leiby A**, Khan S, Corao D. Clinical challenges and images in GI. Collagenous gastroduodenocolitis. *Gastroenterology* 2008; **135**: 17, 327 [PMID: 18555018 DOI: 10.1053/j.gastro.2008.06.007]
30 **Park S**, Kim DH, Choe YH, Suh YL. Collagenous gastritis in a Korean child: a case report. *J Korean Med Sci* 2005; **20**: 146-149 [PMID: 15716621 DOI: 10.3346/jkms.2005.20.1.146]
31 **Pulimood AB**, Ramakrishna BS, Mathan MM. Collagenous gastritis and collagenous colitis: a report with sequential histological and ultrastructural findings. *Gut* 1999; **44**: 881-885 [PMID: 10323893 DOI: 10.1136/gut.44.6.881]
32 **Jin X**, Koike T, Chiba T, Kondo Y, Ara N, Uno K, Asano N, Iijima K, Imatani A, Watanabe M, Shirane A, Shimosegawa T. Collagenous gastritis. *Dig Endosc* 2013; **25**: 547-549 [PMID: 23363075 DOI: 10.1111/j.1443-1661.2012.01391.x]
33 **Jain R**, Chetty R. Collagenous gastritis. *Int J Surg Pathol* 2010; **18**: 534-536 [PMID: 19103610 DOI: 10.1177/1066896908329588]
34 **Kamimura K**, Kobayashi M, Narisawa R, Watanabe H, Sato Y, Honma T, Sekine A, Aoyagi Y. Collagenous gastritis: endoscopic and pathologic evaluation of the nodularity of gastric mucosa. *Dig Dis Sci* 2007; **52**: 995-1000 [PMID: 17342397 DOI: 10.1007/s10620-006-9278-y]
35 **Wang HL**, Shah AG, Yerian LM, Cohen RD, Hart J. Collagenous gastritis: an unusual association with profound weight loss. *Arch Pathol Lab Med* 2004; **128**: 229-232 [PMID: 14736276 DOI: 10.1043/1543-2165(2004)128]
36 **Stancu M**, De Petris G, Palumbo TP, Lev R. Collagenous gastritis associated with lymphocytic gastritis and celiac disease. *Arch Pathol Lab Med* 2001; **125**: 1579-1584 [PMID: 11735694 DOI: 10.1043/0003-9985(2001)125]
37 **Vesoulis Z**, Lozanski G, Ravichandran P, Esber E. Collagenous gastritis: a case report, morphologic evaluation, and review. *Mod Pathol* 2000; **13**: 591-596 [PMID: 10824933 DOI: 10.1038/modpathol.3880101]
38 **Mandaliya R**, DiMarino AJ, Abraham S, Burkart A, Cohene S. Collagenous gastritis a rare disorder in search of a disease. *GR* 2013; **6**: 139-144
39 **Tanabe J**, Yasumaru M, Tsujimoto M, Iijima H, Hiyama S, Nishio A, Sasayama Y, Kawai N, Oshita M, Abe T, Kawano S. A case of collagenous gastritis resembling nodular gastritis in endoscopic appearance. *Clin J Gastroenterol* 2013; **6**: 442-446
40 **Soeda A**, Mamiya T, Hiroshima Y, Sugiyama H, Shidara S, Dai Y, Nakahara A, Ikezawa K. Collagenous gastroduodenitis coexisting repeated Dieulafoy ulcer: A case report and review of collagenous gastritis and gastroduodenitis without colonic involvement. *Clin J Gastroenterol* 2014; In press
41 **Kobayashi M**, Sato Y, Kamimura K, Narisawa R, Sekine A, Aoyagi Y, Ajioka Y, Watanabe H. Collagenous gastritis, a counterpart of collagenous colitis: Reveiew of Japanese case reports. *Stomach and Intestine (Tokyo)* 2009; **44**: 2019-2028
42 **Arnason T**, Brown IS, Goldsmith JD, Anderson W, O'Brien BH, Wilson C, Winter H, Lauwers GY. Collagenous gastritis: a morphologic and immunohistochemical study of 40 patients. *Mod Pathol* 2014; Epub ahead of print [PMID: 25234289 DOI: 10.1038/modpathol.2014.119]

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MINIREVIEWS

Endoscopic treatment of difficult extrahepatic bile duct stones, EPBD or EST: An anatomic view

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Abstract

Large bile duct stone (> 10 mm) or multiple stones (≥ 3) are challenging for endoscopists. Endoscopic sphincterotomy (EST) is a routine therapeutic endoscopic retrograde cholangiopancreatography (ERCP) procedure usually used. It is safe and effective, but severe perforation or massive bleeding are the main causes of mortality. Because of the permanent destroy of Oddi sphincter, the use of EST is still controversial. Endoscopic papillary balloon dilation (EPBD) gives another way to open the sphincter. Less incidence of bleeding, perforation and partly preserving the Oddi sphincter's function are the main advantages. But high incidence of post-ERCP pancreatitis becomes a predominant problem. According to the anatomical feature of Oddi sphincter, limited EST + EPBD seems a more reasonable procedure. Compared to the former two procedures, it makes the stone extraction process much easier with lower incidences of short-term and long-term complications.

Key words: Endoscopic retrograde cholangiopancreatography; Common bile duct stone; Endoscopic sphincterotomy; Endoscopic papillary balloon dilation

Core tip: This review describes endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD) and limited EST + EPBD in the treatment of difficult bile duct stones. We analyze the advantages and disadvantages of these procedures from a unique anatomic view. Limited EST + EPBD may be the most reasonable procedure with the highest successful rate and the lowest incidence of complications.

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INTRODUCTION

Endoscopic sphincterotomy (EST) which was developed from the 70's of last century has been widely used in

therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for a few decades. It is a safe and effective method for the treatment of extrahepatic bile duct stones. Although the short-term complications are decreased with the development of technique and equipment, massive bleeding and perforation are still the main causes for patients' death. As an operation which destroys the Oddi sphincter permanently, the use of EST is controversial. The long-term complications, such as intestinal content reflux, biliary tract inflammation and stone recurrence, are the grounds of argument for those who object the use of EST. In 1982, Staritz treated common bile duct stones by endoscopic papillary balloon dilation (EPBD) successfully. Since then, many authors published reports on the benefits of EPBD and their outcome were almost comparable to EST. Compared with EST, EPBD was easier to operate and of less incidence of bleeding and perforation. Most of all, it might preserve the function of the Oddi sphincter. But soon the high incidence of post ERCP pancreatitis (PEP) reported by DiSario *et al*[1] and his colleagues after a series of multicenter studies questioned the value of this technique. Their results showed that 15%-20% patients developed PEP after EPBD and 2 patients died of severe pancreatitis and EPBD was the only reason for PEP. Incomplete dilation of the papilla, intramucosal bleeding and local edema were thought to be the main causes. Due to the high risk of PEP, most of the endoscopists in North America abandoned this method. But EPBD was still used in Europe and East Asia. Recently some authors report that with large balloon ($\geqslant$ 10 mm) and long term (3 to 5 min) could prominently decreased the incidence of PEP after EPBD compared to the traditional small balloon and short term (< 1 min) procedure. More recent reports recommend the combination of limited EST + EPBD and it seems to be a more reasonable technique.

A WIDE OPENING IS CRUCIAL FOR A SUCCESSFUL STONE EXTRACTION

The treatment of a large bile duct stone (> 10 mm) or multiple stones sometimes appears to be a difficult experience for endoscopists. How to get the opening as wide as possible is the key factor for a successful treatment. To understand the difference between these 3 techniques, some further understanding should be made on the anatomy of the Oddi sphincter. It is a very complicated muscle structure which is composed of sphincter choledochus, sphincter pancreaticus, sphincter ampullae and some longitudinal bundles. In most human beings, the muscle fibers around the orifice of the papilla and the one passing through the duodenum wall are dense and thick. They are the main barrier for stone extraction like two dense rings in the papilla (Figure 1).

It is usually defined that the tunnel starts from the distal portion of the bile duct to the orifice of the papilla as the stone extraction tunnel (SET). Based upon the anatomy described above, we divide the tunnel into two segments: the distal bile duct and the intra-mural portion of the Oddi sphincter constitute the proximal segment, which contains the proximal ring, and the intra-duodenal portion of the papilla forms the distal segment which contains the distal ring around the orifice (Figure 1). EST, EPBD and limited EST + EPBD have different effects on that tunnel. Traditional EST cuts almost the entire distal segment from the orifice up close to the duodenal wall. EPBD dilates the total SET. Limited EST opens the distal portion of the intraluminal papilla and at the same time EPBD dilates the rest portion. Analyzing based on our "2-ring" theory, EST opens the distal ring, shortens SET while does nothing on the proximal ring. EPBD dilates the entire SET including 2 rings but keep the whole structure intact. Limited EST + EPBD cut the distal ring to shorten SET and dilate the proximal ring as well. So the combination procedure may be better to access a wide opening of SET from the anatomical view.

Poincloux *et al*[2] studied 64 cases of limited EST + EPBD for difficult bile duct stones retrospectively. The successful rate in the first attempt was 95.3% without the use of mechanical lithotripsy (ML). Stefanidis *et al*[3] did a prospective study on EST + EPBD and EST + ML for the treatment of large stones (> 12 mm). There was no difference between the two groups of the successful rate in the first attempt (97.7% *vs* 91.1%, $P > 0.05$). It was concluded that EST + EPBD decreased the frequency of ML usage. Another RCT study[4] shows that there's no difference on the successful rate between limited EST+EPBD and EST group. However, the frequency of ML usage is much lower in the former group (28.8% *vs* 46.2%, $P = 0.028$) and the difference becomes more prominent when the diameter of the stones are beyond 15 mm (58.1% *vs* 90.9%, $P = 0.002$).

Reviewing the recent 5-year reports on simple EPBD in treating difficult bile duct stones, the successful rate in the first attempt was 65.8%-92.7% and ML was frequently used[5-8], which indicates the effects are not as good as EST and EST + EPBD.

MORE PATENT THE PANCREATIC OUTFLOW, LESS POST-ERCP PANCREATITIS

Although most of post-ERCP pancreatitis (PEP) cases are mild, it is a common early complication after ERCP intervention. Studies on early EPBD treatment showed a higher incidence of PEP when compared with EST, especially for the severe PEP. Obstruction of the outflow of pancreas aroused by intra-mucosa bleeding and/or local edema after EPBD is assumed to be the main cause. But some authors think that the procedures before EPBD, such as difficult cannulation, guidewire runing into the pancreatic duct repeatedly, opacification of the pancreatic duct or even ML are the

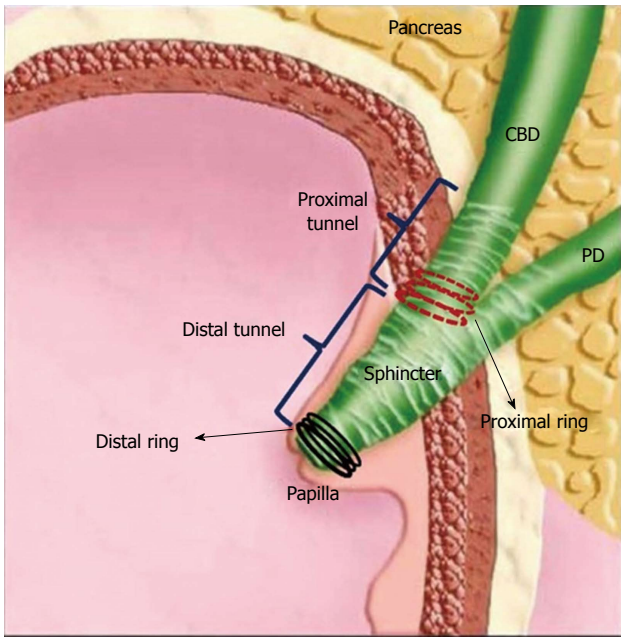

Figure 1 The anatomy of Oddi sphincter and stone extraction tunnel.

key factors for PEP. To prove this hypothesis, Seo *et al*[9] designed an interesting study. Fifty-six antegrade balloon dilation of the papilla through the PTCD method were done for the treatment of common bile duct stones. Two hundred and eight cases of EPBD of the same period were put into the control group. Except for 4 cases of hyperamylasemia, there was no pancreatitis in the experimental group, but the PEP and hyperamylasemia rate was 6.7% (including 1 severe type) and 29.8% respectively in control group. But this hypothesis can't explain why there is a lower incidence of PEP in the EST group when the similar pre-EPBD procedures exists. Reviewing some early reports on EPBD, we can find that the incidence of PEP was as high as 15%-20%. Most of these studies utilized short-term (< 1 min) dilation of the Oddi sphincter with small diameter balloons. Incomplete dilations brought difficulties in stone extraction and resulted in high incidence of ML usage. The subsequent intra-mucosa bleeding and/or local edema around the pancreatic orifice became the main cause of pancreatic outflow obstruction and thus PEP. Comparing to the incomplete short-term dilation with small balloons, EST shortens SET and makes a wider opening which facilitates stone extraction. Therefore, it leads to less edema and eventually a lower incidence of PEP.

Recently, there has been a great development in the EPBD therapy. Long term (3-5 min) dilation with large balloon (12-20 mm) is replacing the old method. Complete dilation results in a total paralysis of the sphincter. It not only makes the extraction easier, but also guarantees a patent bilio-pancreatic outflow for a period of time. Limited EST with long-term large balloon dilation is more widely accepted now, especially in East Asia. This operation is recommended for that it not only opens the distal ring to shorten SET, but also dilates the proximal ring. The bilio-pancreatic outflow is more patent than that made by EST because EST has done nothing to the proximal ring. Although it is called "limited", the cutting edge can usually reach or even exceed the pancreatic orifice. So the subsequent balloon stress maybe only focused on the proximal ring, which may alleviate the extent of edema around the pancreatic orifice.

The recent reports on large balloon and long-term EPBD with or without EST indicate that the incidence of PEP is 5% and there's no significant difference when compares to EST. Park *et al*[10] published a multicenter retrospective studying which EPBD with or without limited EST were used to treat 964 cases of large (> 10 mm) common bile duct stones. Their result confirms that the incidence of PEP has an inverse correlation to the diameter of the balloon. We don't agree that "the bigger, the better" can be the principle for choosing a balloon caliber. The common consensus is that the adequate diameter of a balloon should at least be equal to that of the biggest stone. Furthermore, EPBD is not recommended for the patients without bile duct dilation and those with distal bile duct stricture[10].

LESS CUTTING, LESS BLEEDING AND LESS PERFORATION

The incidence of bleeding after EST is about 0.8%-2%. Radiologic intervention or surgery may be necessary when massive bleeding occurs. Cirrhosis, coagulopathy and anti-coagulant taking are the contraindications for EST. The early purpose of replacing EST with EPBD is to avoid bleeding and perforation. In Japan, Takahara *et al*[11] reported a 37-case group of bile duct stone patients who were undertaking hemodialysis. Only 2 (5.4%) patients developed bleeding after EPBD. When reviewing the recent Meta-analysis comparing EST and EPBD, it is showed that EST has a higher incidence of bleeding.

According to the anatomy of vessel distribution around Oddi sphincter, the small vessels are usually located at the roof of the papilla just close to the duodenal wall. The territory from 11 o'clock to 1 o' clock direction is recommended for a safe EST. In order to get a large outlet for stone extraction, total EST is recommended to extend the incision up close to the duodenal wall, as a result bleeding cannot be totally avoided. Limited EST only cut the distal ring and leave the proximal portion intact to keep a distance from these vessels, so bleeding is rare. Park's *et al*[10] study demonstrated this hypothesis. They found that complete EST or limited EST is the independent factor that influences the incidence of post-operative bleeding (OR 6.22, $P < 0.001$).

Although the incidence of bleeding after EPBD or limited EST + EPBD is low, the result is unacceptable. Excessive cutting, distal bile duct stricture or inadequate use of a large balloon are the main factors for tearing the mucosa of the lower bile duct apart.

Because the location of the bleeding vessels is very high as described, the uncut structure after EPBD or limited EST + EPBD prevent the endoscopists from visualizing the bleeding point directly under the scope. And finally, there may be multiple bleeding exists when the mucosa is torn apart. These factors make the diagnosis and treatment much challenging. Recurrent hemorrhage is common after radiologic intervention or even surgery. Fully covered metal stent maybe useful in this situation.

IS ODDI SPHINCTER WORTH PROTECTING IN CHOLEDOCHOLITHIASIS?

Besides the advantages for less bleeding and less perforation, preserving the function of Oddi sphincter is another goal of EPBD. According to Kojima's[12] excellent manometry study on patients' sphincter before and after EPBD, he concluded that 70% of the sphincter function was preserved after EPBD.

Changes of bile composition and bacterial infection are well-known causes for bile duct stone formation. But little is known in present about the role of biliary dynamics. We believe that it takes great part in the pathogenesis of choledocholithiasis or even cholecystolithiasis.

The normal functions of Oddi sphincter are: (1) to provide a patent pathway for bile excretion; and (2) to prevent bowel reflux. Either disorder in these 2 aspects may result in stone formation. If the etiology is due to an inadequate patency, EST maybe the correct choice; while if bowel reflux is the main problem, such as the para-papilla diverticulum, it may be more reasonable to do EPBD. Some further evidence-based studies was needed on these interesting topics. But above all, development in atraumatic and repeatable diagnostic methods to evaluate the status of Oddi sphincter was looking forward.

CONCLUSION

In summary, EST + EPBD is a reasonable procedure for difficult bile duct stones. It makes a wide opening of the Oddi sphincter to ensure a high success rate of stone extraction with lower incidence of PEP, bleeding and perforation. The long-term results need further researches on the dynamics study of the biliary tract, especially the Oddi sphincter.

REFERENCES

1 **Disario JA**, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299 [PMID: 15520997]

2 **Poincloux L**, Rouquette O, Privat J, Gorce D, Abergel A, Dapoigny M, Bommelaer G. Large-balloon dilation of the sphincter of Oddi after sphincterotomy or infundibulotomy to extract large calculi or multiple common bile duct stones without using mechanical lithotripsy. *Scand J Gastroenterol* 2013; **48**: 246-251 [PMID: 22229762]

3 **Stefanidis G**, Viazis N, Pleskow D, Manolakopoulos S, Theocharis L, Christodoulou C, Kotsikoros N, Giannousis J, Sgouros S, Rodias M, Katsikani A, Chuttani R. Large balloon dilation vs. mechanical lithotripsy for the management of large bile duct stones: a prospective randomized study. *Am J Gastroenterol* 2011; **106**: 278-285 [PMID: 21045816 DOI: 10.1038/ajg.2010.421]

4 **Teoh AY**, Cheung FK, Hu B, Pan YM, Lai LH, Chiu PW, Wong SK, Chan FK, Lau JY. Randomized trial of endoscopic sphincterotomy with balloon dilation versus endoscopic sphincterotomy alone for removal of bile duct stones. *Gastroenterology* 2013; **144**: 341-345.e1 [PMID: 23085096 DOI: 10.1053/j.gastro.2012.10.027]

5 **Kuo CM**, Chiu YC, Changchien CS, Tai WC, Chuah SK, Hu TH, Kuo YH, Kuo CH. Endoscopic papillary balloon dilation for removal of bile duct stones: evaluation of outcomes and complications in 298 patients. *J Clin Gastroenterol* 2012; **46**: 860-864 [PMID: 23060218 DOI: 10.1097/MCG.0b013e3182617a42]

6 **Youn YH**, Lim HC, Jahng JH, Jang SI, You JH, Park JS, Lee SJ, Lee DK. The increase in balloon size to over 15 mm does not affect the development of pancreatitis after endoscopic papillary large balloon dilatation for bile duct stone removal. *Dig Dis Sci* 2011; **56**: 1572-1577 [PMID: 20945093 DOI: 10.1007/s10620-010-1438-4]

7 **Chan HH**, Lai KH, Lin CK, Tsai WL, Wang EM, Hsu PI, Chen WC, Yu HC, Wang HM, Tsay FW, Tsai CC, Chen IS, Chen YC, Liang HL, Pan HB. Endoscopic papillary large balloon dilation alone without sphincterotomy for the treatment of large common bile duct stones. *BMC Gastroenterol* 2011; **11**: 69 [PMID: 21668994 DOI: 10.1186/1471-230X-11-69]

8 **Jeong S**, Ki SH, Lee DH, Lee JI, Lee JW, Kwon KS, Kim HG, Shin YW, Kim YS. Endoscopic large-balloon sphincteroplasty without preceding sphincterotomy for the removal of large bile duct stones: a preliminary study. *Gastrointest Endosc* 2009; **70**: 915-922 [PMID: 19647241 DOI: 10.1016/j.gie.2009.04.042]

9 **Seo YR**, Moon JH, Choi HJ, Kim DC, Lee TH, Cha SW, Cho YD, Park SH, Kim SJ. Papillary balloon dilation is not itself a cause of post-endoscopic retrograde cholangiopancreatography pancreatitis; results of anterograde and retrograde papillary balloon dilation. *J Gastroenterol Hepatol* 2013; **28**: 1416-1421 [PMID: 23701518 DOI: 10.1111/jgh.12277]

10 **Park SJ**, Kim JH, Hwang JC, Kim HG, Lee DH, Jeong S, Cha SW, Cho YD, Kim HJ, Kim JH, Moon JH, Park SH, Itoi T, Isayama H, Kogure H, Lee SJ, Jung KT, Lee HS, Baron TH, Lee DK. Factors predictive of adverse events following endoscopic papillary large balloon dilation: results from a multicenter series. *Dig Dis Sci* 2013; **58**: 1100-1109 [PMID: 23225136 DOI: 10.1007/s10620-012-2494-8]

11 **Takahara N**, Isayama H, Sasaki T, Tsujino T, Toda N, Sasahira N, Mizuno S, Kawakubo K, Kogure H, Yamamoto N, Nakai Y, Hirano K, Tada M, Omata M, Koike K. Endoscopic papillary balloon dilation for bile duct stones in patients on hemodialysis. *J Gastroenterol* 2012; **47**: 918-923 [PMID: 22354661 DOI: 10.1007/s00535-012-0551-x]

12 **Kojima Y**, Nakagawa H, Miyata A, Hirai T, Ohyama I, Okada A, Hiramatsu T, Ohhara Y, Kuwahara T. Long-term prognosis of bile duct stones: endoscopic papillary balloon dilatation versus endoscopic sphincterotomy. *Dig Endosc* 2010; **22**: 21-24 [PMID: 20078660 DOI: 10.1111/j.1443-1661.2009.00913.x]

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ORIGINAL ARTICLE

Retrospective Study

Rotational assisted endoscopic retrograde cholangiopancreatography in patients with reconstructive gastrointestinal surgical anatomy

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Author contributions: All authors helped equally in: Substantial contributions to the conception or design of the work including the acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: The study was reviewed and approved by the Duke University Health System (DUHS) Institutional Review Board (IRB).

Informed consent: The study is a retrospective review. Only general demographic information in regards to the patients was obtained. No informed consent was obtained from involved persons. A waiver of consent was filled and approved by DUHS IRB.

Conflict-of-interest: All authors declare that there is no conflict of interest.

Data sharing: No additional data are available.

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Abstract

AIM: To evaluate the success rates of performing therapy utilizing a rotational assisted enteroscopy device in endoscopic retrograde cholangiopancreatography (ERCP) in surgically altered anatomy patients.

METHODS: Between June 1, 2009 and November 8, 2012, we performed 42 ERCPs with the use of rotational enteroscopy for patients with altered anatomy (39 with gastric bypass Roux-en-Y, 2 with Billroth Ⅱ gastrectomy, and 1 with hepaticojejunostomy associated with liver transplant). The indications for ERCP were: choledocholithiasis: 13 of 42 (30.9%), biliary obstruction suggested on imaging: 20 of 42 (47.6%), suspected sphincter of Oddi dysfunction: 4 of 42 (9.5%), abnormal liver enzymes: 1 of 42 (2.4%), ascending cholangitis: 2 of 42 (4.8%), and bile leak: 2 of 42 (4.8%). All procedures were completed with the Olympus SIF-Q180 enteroscope and the Endo-Ease Discovery SB overtube produced by Spirus Medical.

RESULTS: Successful visualization of the major ampulla was accomplished in 32 of 42 procedures (76.2%). Cannulation of the bile duct was successful in 26 of 32 procedures reaching the major ampulla (81.3%). Successful therapeutic intervention was completed in 24 of 26 procedures in which the bile

duct was cannulated (92.3%). The overall intention to treat success rate was 64.3%. In terms of cannulation success, the intention to treat success rate was 61.5%. Ten out of forty two patients (23.8%) required admission to the hospital after procedure for abdominal pain and nausea, and 3 of those 10 patients (7.1%) had a diagnosis of post-ERCP pancreatitis. The average hospital stay was 3 d.

CONCLUSION: It is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to alleviate biliary complications in patients with altered surgical anatomy.

Key words: Gastric bypass; Gastrostomy; Cholangiopancreatography; Endoscopic retrograde; Double-Balloon enteroscopy; Ampulla of vater; Sphincterotomy; Endoscopic; Pancreatitis; Retrospective studies

Core tip: This manuscript shows a single tertiary care center experience in a large number of patients with surgically altered anatomy by evaluating the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing therapy utilizing a rotational assisted enteroscopy device in an endoscopic retrograde cholangiopancreatography. This study will also determine the associated morbidity, mortality, and length of hospitalization associated with the procedures. Given our institutions success rates and minimal complication profile, specialized centers could consider this approach in this rapidly growing population. This will be instrumental in the development of new therapeutic options for patients suffering from this condition.

Zouhairi ME, Watson JB, Desai SV, Swartz DK, Castillo-Roth A, Haque M, Jowell PS, Branch MS, Burbridge RA. Rotational assisted endoscopic retrograde cholangiopancreatography in patients with reconstructive gastrointestinal surgical anatomy. *World J Gastrointest Endosc* 2015; 7(3): 278-282 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/278.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.278

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard in both diagnosis and therapeutic management of pancreato-biliary diseases. However, patients with surgically altered anatomy present a unique endoscopic challenge. In patients with normal anatomy, rate of successful cannulation and sphincterotomy by expert endoscopists is greater than ninety percent[1]. In patients who have had reconstructive gastrointestinal surgery, reaching the ampulla and subsequently performing therapy during ERCP has been reported in a multicenter study to be 63%[2]. Additionally, as the obesity epidemic has widened in the United States, patients with altered anatomy due to bariatric surgery are increasingly presenting with the need for evaluation for pancreato-biliary disease[3].

Multiple methods have been described to gain access to the biliary tract in post surgical patients, which is particularly challenging because the standard duodenoscope cannot reach the ampulla due to increased distance of the Roux limb. Methods to gain biliary access with a standard duodenoscope, such as a surgically created gastrostomy have been previously described[4-6]. Non-surgical endoscopic methods using different types of enteroscopy techniques have also been described. These endoscopic techniques include double-balloon, single-balloon, and rotational assisted-ERCP (RA-ERCP)[7-9].

The goal of this retrospective study is to review a single tertiary care center experience in RA-ERCP in patients with reconstructive gastrointestinal surgery. Outcomes measured include the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing a complete ERCP. Additionally, the associated morbidity, mortality, and length of hospitalization associated with RA-ERCP were measured.

MATERIALS AND METHODS

Study and patients

An IRB approved retrospective review of all patients undergoing rotational assisted ERCP was performed.

Between June 1, 2009 and November 8, 2012, a total of 42 RA-ERCPs were attempted for patients with altered anatomy. Thirty-three of these patients underwent Roux-en-Y gastric bypass, 2 underwent Billroth Ⅱ gastrectomy, and 1 underwent hepaticojejunostomy associated with liver transplant. A total of 6 patients had repeat procedures.

Procedures

Sedation for the procedures were either moderate sedation (9 patients) or general anesthesia (33 patients) with the positioning of all patients in the prone position. An attending advanced endoscopist performed all procedures with the assistance of the advanced endoscopy fellow. A total of 4 attending physicians with experience in rotational assisted ERCP performed the procedures.

All RA-ERCPs were performed using an Olympus SIF-Q180 enteroscope and the Endo-Ease Discovery SB overtube manufactured by Spirus Medical.

Patients were not randomized, as the procedure was chosen based on availability and physician discretion. Procedural time for RA-ERCP was determined from the onset of the "time-out" patient verification to the time

Table 1 Patient characteristics

No. of patients	36
No. of ERCPs	42
Age	49.3
Sex	M = 2, F = 34
BMI	36.3
Roux-en-Y surgery patients	33
Billroth Ⅱ surgery patients	2
Hepaticojejunostomy associated with liver transplant	1

M: Male; F: Female; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Indications for endoscopic retrograde cholangiopancreatography

Suspected gallstones/choledocholithiasis	13
Sphincter of Oddi dysfunction Ⅰ / Ⅱ	1/3
Biliary obstruction on imaging	20
Ascending cholangitis	2
Biliary obstruction with negative imaging	1
Bile leak	2

the patient arrived in the recovery bay.

Statistical analysis

The statistical methods of this study were reviewed by Majed El Zouhairi, MD and Rebecca Burbridge, MD from Duke University Medical Center.

RESULTS

Rotational enteroscopy was performed in forty-two separate procedures, in thirty-six patients with altered anatomy. Thirty-four patients were women (94.4%) and the mean age was 49.3 (range 29-75) (Table 1). The indications for ERCP were: biliary obstruction suggested on imaging 20 of 42 (47.6%), choledocholithiasis 13 of 42 (30.9%), suspected sphincter of Oddi dysfunction 4 of 42 (9.5%), ascending cholangitis 2 of 42 (4.8%), bile leak 2 of 42 (4.8%), and abnormal liver enzymes 1 of 42 (2.4%) (Table 2). The ability to reach and visualize the major ampulla was successful in 32 of 42 procedures (76.2%) (Figure 1). Attempted cannulation of the bile duct was performed in 29 out of the 32 procedures which successfully reached the major ampulla, with a subsequent bile duct cannulation rate of 89.7% (Figure 2). No attempt was made to cannulate the bile duct in three patients because procedures were only intended to remove previously placed stents. The reason for failed cannulation in the three patients in whom we were not able to cannulate the bile duct despite reaching the ampulla was an ampullary polyp (1 patient) and biliary stricture (2 patients). Successful therapeutic intervention including, but not limited to, sphincterotomy, stone removal, bile duct/pancreatic duct stent placement, balloon sweeping, and brushing was completed in 24 of 26 procedures

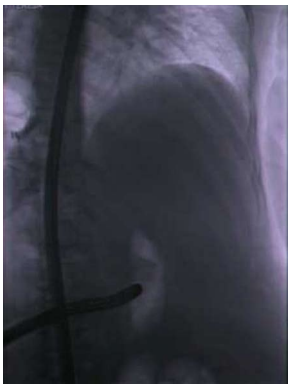

Figure 1 Scout film with the positioning of the scope.

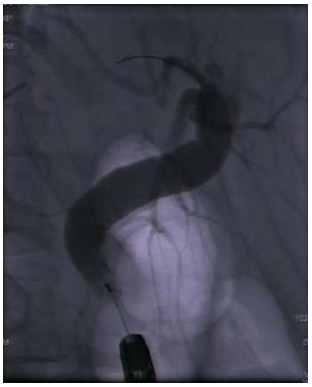

Figure 2 Cholangiogram.

in which the bile duct was cannulated (92.3%) (Figure 3). Of the total 42 cases, there were 15 failed cases, and 27 successful procedures, therefore the overall intention to treat success rate was 64.3%. In terms of cannulation success, 24 of 39 attempts at cannulation were successful, with an intention to treat success rate of 61.5%.

Ten patients out of 42 procedures (23.8%) required hospital admission for abdominal pain and nausea following the procedure. Three of those 10 patients (7.1%) had a diagnosis of post-ERCP pancreatitis. The average hospital stay was 3 d (Table 3). There were no overtube related complications.

DISCUSSION

Surgically altered anatomy has become increasingly more common in the United States, particularly due to bariatric surgery. Reaching the ampulla in patients with surgically altered anatomy remains challenging even for skilled endoscopists despite advances in deep small bowel enteroscopy. Currently, the standard of care for pancreato-biliary disease in these patients often involves surgical assistance to help access the major ampulla. Success rates with single-balloon[10-13] and double-balloon enteroscopy systems[2,14-19] have been reported to range from 60% to 88%[2]. In limited studies, RA-ERCP has been shown to be a promising

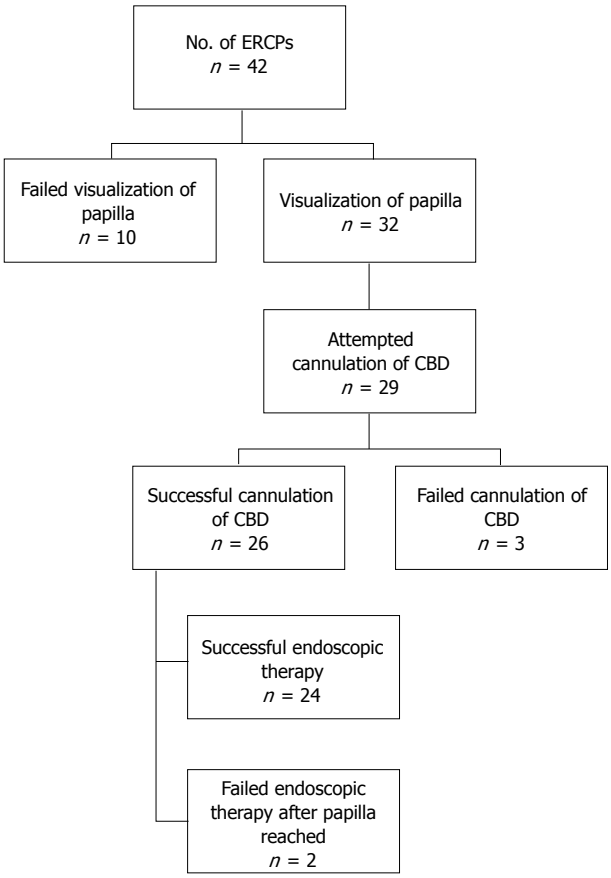

Figure 3 Outcomes. ERCP: Endoscopic retrograde cholangiopancreatography.

technique for pancreato-biliary access in post surgical patients. Hegde *et al*[7] reported that RA-ERCP allowed successful cannulation in 2 patients after double-balloon assisted ERCP had failed, but that it was more time-consuming. Al-Lehibi *et al*[8], also noted that RA-ERCP was successful in 5 of 6 cases. A recent prospective study reported in 2012 by Wagh *et al*[9] on 13 patients showed that cannulation of the desired duct and endoscopic therapy using RA-ERCP in patients with surgically altered anatomy was successful in 90% of the procedures if the papilla/duct-enterostomy was reached.

A recent multi-center retrospective study published in January 2013 by Shah *et al*[2] compared ERCP success in 129 patients with surgically altered anatomy utilizing single-balloon (SBE), double-balloon (DBE), or rotational overtube enteroscopy. Fifty-seven RA-ERCP cases were performed with an intention to treat success rate of 63%, defined as successful planned therapeutic intervention. They concluded that therapeutic success in long-limb surgical bypass was similar irregardless of the endoscopic method used.

Our study is the largest single-center experience evaluating RA-ERCP in patients with reconstructed gastrointestinal anatomy. We noted RA-ERCP procedural success rate in visualizing the ampulla of 76.2%, cannulating the bile duct in procedures reaching the major ampulla of 81.3%, and successfully completing

Table 3 Complications

Adverse events	10
No. of admission	10
Length of hospital stay after admission (d)	3

therapeutic interventions after cannulating the major ampulla of 92.3% with an overall intention to treat success rate of 61.5%. This seems consistent with the rate published by Shah *et al*[2], and would suggest that RA-ERCP is on par with other non-surgical endoscopic techniques.

Limitations of this study include the lack of direct comparison with other deep enteroscopy techniques. A second limitation is that all procedures were performed in a tertiary-care center which may not be generalizable to smaller gastroenterology practices which serve a local community. Additionally, the strength of one specific endoscopic technique for non-ERCP enteroscopy has not been consistently demonstrated. The concept that experience may play an important role in success is supported by data from the non-ERCP enteroscopy literature. For example the efficacy of double balloon compared to rotation assisted enteroscopy is still debatable and experience in either modality may be more important than the type of enteroscopy modality chosen[20-22].

Given our institution's success rates and minimal complication profile, we believe it is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to evaluate pancreato-biliary diseases in patients with altered surgical anatomy. Our data, as well as other smaller studies, have confirmed the safety and relative efficacy of this approach. In determining the method of endoscopic approach to ERCP in post surgical patients, relative experience with other enteroscopy modalities such as DBE or SBE should also be considered.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) has been a mainstay in the diagnosis and management of pancreato-biliary diseases. With the use of a standard duodenoscope, success rates are greater than ninety percent in patients with normal gastrointestinal anatomy. However, reaching the ampulla and subsequently performing therapy during ERCP is difficult in patients with surgically altered anatomy. Utilizing a rotational enteroscopy device to assist in reaching the ampulla in this population may increase the chances of being able to successfully complete the procedure.

Research frontiers

There have been only a few small number of studies examining the use of RA-ERCP in approaching biliary complications in patients with Roux-en-Y gastric bypass surgery.

Innovations and breakthroughs

This manuscript shows a single tertiary care center experience in a large number of patients with surgically altered anatomy by evaluating the success rates of reaching the major ampulla, cannulating the bile duct, and subsequently performing therapy utilizing a rotational assisted enteroscopy device in order to complete an ERCP. This study will also determine the associated morbidity, mortality, and length of hospitalization associated with the procedures.

Applications

Surgically altered anatomy has become increasingly more common in the United States, particularly due to bariatric surgery. Currently, the standard of care for pancreatico-biliary complications in these patients often involves surgical assistance to help access the major ampulla. Given our institutions success rates and minimal complication profile, the authors believe it is reasonable to consider an attempt at rotational assisted ERCP prior to a surgical intervention to alleviate biliary complications in patients with altered surgical anatomy.

Terminology

ERCP; rotational assisted-ERCP (RA-ERCP); single-balloon enteroscopy (SBE); double-balloon enteroscopy (DBE).

Peer-review

This paper is interesting.

REFERENCES

1 **Huibregtse K**, Kimmey MB. Endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy and stone removal, and endoscopic biliary and pancreatic drainage. In: Yamada T, editor. Textbook of gastroenterology. Philadelphia: J.B. Lippincott, 1995: 2590-2617

2 **Shah RJ**, Smolkin M, Yen R, Ross A, Kozarek RA, Howell DA, Bakis G, Jonnalagadda SS, Al-Lehibi AA, Hardy A, Morgan DR, Sethi A, Stevens PD, Akerman PA, Thakkar SJ, Brauer BC. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). *Gastrointest Endosc* 2013; **77**: 593-600 [PMID: 23290720 DOI: 10.1016/j.gie.2012.10.015]

3 **Adams TD**, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; **357**: 753-761 [PMID: 17715409 DOI: 10.1056/NEJMoa066603]

4 **Baron TH**, Vickers SM. Surgical gastrostomy placement as access for diagnostic and therapeutic ERCP. *Gastrointest Endosc* 1998; **48**: 640-641 [PMID: 9852460 DOI: 10.1016/S0016-5107(98)70052-5]

5 **Peters M**, Papasavas PK, Caushaj PF, Kania RJ, Gagné DJ. Laparoscopic transgastric endoscopic retrograde cholangiopancreatography for benign common bile duct stricture after Roux-en-Y gastric bypass. *Surg Endosc* 2002; **16**: 1106 [PMID: 11988790 DOI: 10.1007/s00464-001-4180-3]

6 **Lopes TL**, Wilcox CM. Endoscopic retrograde cholangiopancreatography in patients with Roux-en-Y anatomy. *Gastroenterol Clin North Am* 2010; **39**: 99-107 [PMID: 20202583 DOI: 10.1016/j.gtc.2009.12.008]

7 **Hegde SR**, Downey S, Iffrig K, Heller SJ, Tokar JF, Haluszka O. Overtube-assisted ERCP in patients with surgically altered anatomy: a single center one-year experience [abstract]. *Gastrointest Endosc* 2009; **69** AB193 [DOI: 10.1016/j.gie.2009.03.413]

8 **Al-Lehibi AH**, Kumar N, Sayuk GS, Ammar T, Murad F, Mullady D, Early DS, Azar RR, Edmundowicz SA, Jonnalagadda SS. Success rates for endoscopic retrograde cholangiopancreatography (ERCP) in patients with altered anatomy from prior surgical intervention [abstract]. *Gastrointest Endosc* 2010; **71**: AB228 [DOI: 10.1016/j.gie.2010.03.463]

9 **Wagh MS**, Draganov PV. Prospective evaluation of spiral overtube-assisted ERCP in patients with surgically altered anatomy. *Gastrointest Endosc* 2012; **76**: 439-443 [PMID: 22817798 DOI: 10.1016/j.gie.2012.04.444]

10 **Dellon ES**, Kohn GP, Morgan DR, Grimm IS. Endoscopic retrograde cholangiopancreatography with single-balloon enteroscopy is feasible in patients with a prior Roux-en-Y anastomosis. *Dig Dis Sci* 2009; **54**: 1798-1803 [PMID: 18989776]

11 **Mönkemüller K**, Fry LC, Bellutti M, Neumann H, Malfertheiner P. ERCP using single-balloon instead of double-balloon enteroscopy in patients with Roux-en-Y anastomosis. *Endoscopy* 2008; **40** Suppl 2: E19-E20 [PMID: 18278720 DOI: 10.1055/s-2007-966949]

12 **Neumann H**, Fry LC, Meyer F, Malfertheiner P, Monkemuller K. Endoscopic retrograde cholangiopancreatography using the single balloon enteroscope technique in patients with Roux-en-Y anastomosis. *Digestion* 2009; **80**: 52-57 [PMID: 19478486 DOI: 10.1159/000216351]

13 **Itoi T**, Ishii K, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Tsuji S, Ikeuchi N, Umeda J, Moriyasu F. Single-balloon enteroscopy-assisted ERCP in patients with Billroth II gastrectomy or Roux-en-Y anastomosis (with video). *Am J Gastroenterol* 2010; **105**: 93-99 [PMID: 19809409 DOI: 10.1038/ajg.2009.559]

14 **Emmett DS**, Mallat DB. Double-balloon ERCP in patients who have undergone Roux-en-Y surgery: a case series. *Gastrointest Endosc* 2007; **66**: 1038-1041 [PMID: 17963892 DOI: 10.1016/j.gie.2007.06.056]

15 **Aabakken L**, Bretthauer M, Line PD. Double-balloon enteroscopy for endoscopic retrograde cholangiography in patients with a Roux-en-Y anastomosis. *Endoscopy* 2007; **39**: 1068-1071 [PMID: 18072058 DOI: 10.1055/s-2007-966841]

16 **Mönkemüller K**, Bellutti M, Neumann H, Malfertheiner P. Therapeutic ERCP with the double-balloon enteroscope in patients with Roux-en-Y anastomosis. *Gastrointest Endosc* 2008; **67**: 992-996 [PMID: 18279869 DOI: 10.1016/j.gie.2007.10.023]

17 **Maaser C**, Lenze F, Bokemeyer M, Ullerich H, Domagk D, Bruewer M, Luegering A, Domschke W, Kucharzik T. Double balloon enteroscopy: a useful tool for diagnostic and therapeutic procedures in the pancreaticobiliary system. *Am J Gastroenterol* 2008; **103**: 894-900 [PMID: 18371136 DOI: 10.1111/j.1572-0241.2007.01745.x]

18 **Chu YC**, Yang CC, Yeh YH, Chen CH, Yueh SK. Double-balloon enteroscopy application in biliary tract disease-its therapeutic and diagnostic functions. *Gastrointest Endosc* 2008; **68**: 585-591 [PMID: 18561917 DOI: 10.1016/j.gie.2008.03.1083]

19 **Iwamoto S**, Ryozawa S, Yamamoto H, Taba K, Ishigaki N, Harano M, Iwano H, Sakaida I. Double balloon endoscope facilitates endoscopic retrograde cholangiopancreatography in roux-en-y anastomosis patients. *Dig Endosc* 2010; **22**: 64-68 [PMID: 20078669 DOI: 10.1111/j.1443-1661.2009.00920.x]

20 **Khashab MA**, Lennon AM, Dunbar KB, Singh VK, Chandrasekhara V, Giday S, Canto MI, Buscaglia JM, Kapoor S, Shin EJ, Kalloo AN, Okolo PI. A comparative evaluation of single-balloon enteroscopy and spiral enteroscopy for patients with midgut disorders. *Gastrointest Endosc* 2010; **72**: 766-772 [PMID: 20619404 DOI: 10.1016/j.gie.2010.04.043]

21 **Messer I**, May A, Manner H, Ell C. Prospective, randomized, single-center trial comparing double-balloon enteroscopy and spiral enteroscopy in patients with suspected small-bowel disorders. *Gastrointest Endosc* 2013; **77**: 241-249 [PMID: 23043851 DOI: 10.1016/j.gie.2012.08.020]

22 **Akerman PA**. Spiral enteroscopy versus double-balloon enteroscopy: choosing the right tool for the job. *Gastrointest Endosc* 2013; **77**: 252-254 [PMID: 23317690 DOI: 10.1016/j.gie.2012.11.010]

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SYSTEMATIC REVIEWS

Endoscopic ultrasound-guided biliary intervention in patients with surgically altered anatomy

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Abstract

AIM: To evaluate the efficacy of endoscopic ultrasound guided biliary drainage (EUS-BD) in patients with surgically altered anatomies.

METHODS: We performed a search of the MEDLINE database for studies published between 2001 to July 2014 reporting on EUS-BD in patients with surgically altered anatomy using the terms "EUS drainage" and "altered anatomy". All relevant articles were accessed in full text. A manual search of the reference lists of relevant retrieved articles was also performed. Only full-text English papers were included. Data regarding age, gender, diagnosis, method of EUS-BD and intervention, type of altered anatomy, technical success, clinical success, and complications were extracted and collected. Anatomic alterations were categorized as: group 1, Billroth Ⅰ; group 2, Billroth Ⅱ; group 4, Roux-en-Y with gastric bypass; and group 3, all other types.

RESULTS: Twenty three articles identified in the literature search, three reports were from the same group with different numbers of cases. In total, 101 cases of EUS-BD in patients with altered anatomy were identified. Twenty-seven cases had no information and were excluded. Seventy four cases were included for analysis. Data of EUS-BD in patients categorized as group 1, 2 and 4 were limited with 2, 3 and 6 cases with EUS-BD done respectively. Thirty four cases with EUS-BD were reported in group 3. The pooled technical success, clinical success, and complication rates of all reports with available data were 89.18%, 91.07% and 17.5%, respectively. The results are similar to the reported outcomes of EUS-BD in general, however, with limited data of EUS-BD in patients with altered anatomy rendered it difficult to draw a firm conclusion.

CONCLUSION: EUS-BD may be an option for patients with altered anatomy after a failed endoscopic-retrograde-cholangiography in centers with expertise in EUS-BD procedures in a research setting.

Key words: Endoscopic ultrasound-guided anterograde approach; Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-rendezvous technique; Surgically altered anatomy; Overtube-assisted enteroscopy-endoscopic retrograde cholangiopancreatography

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) in patients with surgically altered anatomy is challenging, with a failure rate as high as 26%. Data of endoscopic ultrasound-guided biliary drainage (EUS-BD) in patients with altered anatomy from the literature show a similar efficacy to that of EUS-BD in general. EUS-BD may be selected as an alternative for patients with altered anatomy who failed overtube-assisted enteroscopy-ERCP in centers where the expertise in EUS-BD is available. However, the EUS-BD approach should be performed in a research setting based on the current stage of EUS-BD techniques.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been widely accepted as a standard procedure with a high success rate for the management of biliary disorders[1]. However, conventional ERCP in patients with surgically altered anatomy is technically difficult, and is accompanied by a relatively high rate of complications. In large case series, technical failures varied from 13% to 67%, and the rate of perforation was as high as 18%, with a mortality rate of 3%[2,3]. ERCP with overtube-assisted enteroscopy (OAE-ERCP), with a balloon or spiral overtube, achieved a success rate of approximately 74% and a 3.4% complication rate in patients with surgically altered anatomies[4]. Percutaneous transhepatic biliary drainage (PTBD) is a well-established technique that is usually selected as an alternative in patients with failed ERCP. However, despite the high clinical success rate, the PTBD approach is associated with 0.5%-15% morbidity and 0%-4.9% mortality rates[5].

Endoscopic ultrasound-guided biliary drainage (EUS-BD) was first reported in 2001 by Giovannini *et al*[6]. Subsequently, many groups reported the utilization of EUS-BD with various approaches as an alternative biliary drainage for failed ERCPs, with an average success rate varying from 77% to 94% and complication rate of 19%-27%[7]. This method may be an option for patients with altered anatomy for whom OAE-ERCP is difficult, as reflected by a high failure rate (26%)[4]. However, the role of EUS-BD in patients with altered anatomy and failed ERCP is not well defined, and the suitability of this as an alternative drainage procedure is unclear. This review analyzes the clinical efficacy, complications, clinical implication, and limitations of EUS-BD in patients with surgically altered anatomy from data available in the literature.

MATERIALS AND METHODS

A PubMed search of the MEDLINE database was conducted for articles published between 2001 and July 2014 using the terms "EUS drainage" and "altered anatomy". A manual search of the reference lists of relevant retrieved articles was also performed. Only full-text English papers were included. The computerized endoscopic data at our center were also searched for additional cases of EUS-BD in altered anatomy conducted after our published data[8]. Data regarding age, gender, diagnosis, method of EUS-BD and intervention, type of altered anatomy, technical success, clinical success, and complications were collected.

Classification of EUS-BD techniques

The three main techniques of EUS-guided procedures for biliary drainage that were included were: anterograde EUS-BD, transluminal drainage, and the rendezvous method[7,9,10]. Anterograde EUS-BD involves intervention *via* an anterograde route across the ampulla or anastomosis. Transluminal drainage encompasses transesophageal, transgastric (hepaticogastrostomy), transduodenal (choledochoduodenostomy, EUS-CDS), or transjejunal approaches. The rendezvous method involves EUS-guided placement of a guide-wire across the ampulla or anastomosis that is exchanged with a standard duodenoscope or enteroscope to perform the intervention.

Classification of surgically altered anatomy

Anatomic alterations were categorized as: group 1, Billroth Ⅰ; group 2, Billroth Ⅱ; group 3, Roux-en-Y with pancreaticoduodenectomy (with or without a modified Child procedure), pylorus-preserving pancreaticoduodenectomy, hepaticojejunostomy, choledochojejunostomy, and total or partial gastrectomy, distal gastrectomy without specific anastomosis mentioned, and hepatic and bile duct resection; and group 4, Roux-en-Y with gastric bypass (RY-GB).

Statistical analysis

The descriptive data of age was analyzed by using Minitab 15® and no other statistical analysis was done since this study was a descriptive review.

RESULTS

EUS-BD IN patients with surgically altered anatomy

Of the 23 articles identified in the literature search, three reports were from the same group with different numbers of cases[11-13]. As no details regarding individual cases were available from these three reports, the cases with the same type of surgically

Table 1 Demographics of endoscopic ultrasound-guided biliary drainage patients with altered anatomy[8,11,14,18-32] (*n* = 74)

Characteristic	Value
Age, yr (*n* = 36)	64.14 ± 15.08
Sex, female/male (*n* = 36)	22/14
Diagnosis (*n* = 38)	
Bile duct stone	14
Benign stricture	10
Malignant stricture	11
Gastric cancer	2
Occluded stent	1
Outcome of EUS-BD, *n* (%)	
Clinical success	51 (91.1)
Complications	7 (17.5)
Technical success	66 (89.2)
EUS-BD technique with technical success, *n*	
Anterograde	28
Hepaticogastrostomy	18
Hepaticojejunostomy	2
Hepaticoesophagostomy	1
Rendezvous	3
Unavailable	14

EUS-BD: Endoscopic ultrasound-guided biliary drainage.

altered anatomy and the same diagnosis were treated as one case. In total, 101 cases of EUS-BD in patients with altered anatomy were identified. Only one report was a case series[14], all other reports were case reports or reports of EUS-BD that included normal and altered anatomy patients. Twenty-seven cases had no information and were excluded[12,15-17], leaving 74 patients with altered anatomy who underwent EUS-BD[8,11,14,18-32]. Available demographic and procedural information of these cases is presented in Table 1. Of the 40 cases reporting complications, there were incidences of mild pancreatitis (*n* = 2), mild abdominal pain (*n* = 1), hematoma (*n* = 1), cholangitis (*n* = 1), minor bleeding (*n* = 1), and surgical repositioning of a stent in the peritoneum (*n* = 1), with no mortalities.

EUS-BD in altered anatomy subtypes

The classification of altered anatomy types is listed in Table 2. In group 1, one case of EUS-BD with common bile duct (CBD) stones was reported[25], and EUS-BD was performed in one patient with distal CBD stricture at our center. Both had successful clinical outcomes. There were three cases with EUS-BD in group 2: two cases with malignant stricture and one case with a CBD stone, in whom the EUS-BD failed[11,32].

Within group 3, Roux-en-Y was performed with hepaticojejunostomy (*n* = 10), choledochojejunostomy (*n* = 1), total gastrectomy (*n* = 5), subtotal gastrectomy (*n* = 2), Whipple's operation (*n* = 6), distal gastrectomy (*n* = 2), pylorus-preserving pancreaticoduodenectomy (*n* = 5), pancreaticoduodenectomy with a modified Child procedure (*n* = 2), and hepatic and bile duct resection (*n* = 1)[8,11,14,18-32]. The diagnoses in group 3 included bile duct stones (*n* = 9), benign stricture (*n* = 9), malignant stricture (*n* = 9), occluded metallic stents placed by percutaneous route (*n* = 1), or were unspecified (*n* = 6). The success rates were in the range reported for EUS-BD in general. However, the missing data in a large proportion of patients in this group rendered it difficult to draw a firm conclusion.

Table 2 Results of endoscopic ultrasound-guided biliary drainage in altered anatomy subgroups

Group	Subtype	No. of cases	Technical success	Clinical success	Complications
1	Billroth Ⅰ	2	2	2	0
2	Billroth Ⅱ	3	2	2	0
3	Roux-en-Y	34	33 (97.0%)	23 (92.0%)	5
4	Roux-en-Y gastric bypass	6	6	5	1

Twenty-seven cases with unspecified type and no details available were excluded.

Six cases within group 4 received EUS-BD with RY-GB[33]. These patients all had CBD stones, and stone clearance was achieved with EUS-BD in five of these, with a failure in one with a hematoma.

In 27 cases that were excluded from analysis due to insufficient information[12,15-17], the overall technical success rate (including patients with altered anatomy) varied from 67.2% to 94.0%, the clinical success rate varied from 63.2% to 97.0%, and the complication rate varied from 12.0% to 23.2%.

DISCUSSION

EUS-BD vs PTBD

PTBD is a traditional alternative for patients with a failed ERCP, though it is associated with a risk of complication and significant morbidity[5]. One of the major drawbacks of PTBD is external bile loss, which leads to a decreased total bile pool. Theoretically, maintenance of enterohepatic bile circulation is important for host defense function. Kamiya *et al*[33] reported that bile replacement by oral intake of the externally diverted bile helped restore gut barrier function in patients with bile duct obstruction, but internal drainage is still more physiologic than external drainage. Moreover, the burden to the patients or family members caring for the catheter is considerable, and individuals who bathe twice daily may be disturbed by the inability to do so, thus decreasing their quality of life. In one retrospective study that compared 22 EUS-BD patients with 51 PTBD patients, the procedures showed a similar clinical success, but EUS-BD was associated with fewer adverse events and was less costly in the long term[34]. However, PTBD in their study had a 100% success rate, which was significantly higher than the 86.4% with EUS-BD. Another retrospective study compared 25 cases with EUS-BD with 26 cases with PTBD, and showed that EUS-BD was superior to PTBD in terms of success and complication rates[35]. In contrast, a prospective study showed a similar efficacy between EUS-BD performed

in 13 patients and PTBD in 12 patients[36]. Taken together, these data suggest that EUS-BD is a suitable alternative in patients with failed ERCP, and it may be an option in the centers where EUS-BD is available.

Role of EUS-BD in altered anatomy patients

The available data suggest that EUS-BD is as effective in patients with altered anatomy as in general patients. EUS-BD is still in a state of development, with proper procedural techniques under refinement. Furthermore, EUS-BD for patients with altered anatomy and failed ERCP should be assessed in a research setting to properly define its role. A standardized treatment algorithm for selection of EUS-BD techniques based on the clinical context may improve the outcome[26].

In patients with a Billroth Ⅰ operation, the straight anatomy of the stomach and duodenum cause the tip of a standard duodenoscope to come too close to the papilla, making it difficult to position the ERCP catheter along the axis of the bile duct, leading to a failed procedure in some patients[37]. In patients with Billroth Ⅱ anatomy, OAE-ERCP has an endoscopic success rate of 96% and a successful ERCP rate of 90%[4]. ERCP is the most difficult in patients with RY-GB, and OAE-ERCP has an endoscopic success rate of only 80% and successful ERCP rate of only 70%[4]. In post RY-GB patients with failed OAE-ERCP, laparoscopy-assisted ERCP may be an alternative, as the results in four publications[38-41] demonstrated a high success rate of 90%-100%. However, these studies were limited by the number of patients, longer procedure time, the need for a laparoscopic doctor, and a much higher cost of treatment. The data supporting the role of EUS-BD in groups 1, 2 and 4 were very limited, and need further evaluation.

EUS-BD may be a suitable alternative in patients with failed OAE-ERCP with altered anatomy classified as group 3. In patients with benign stricture, the accepted treatment includes extended multiple plastic stents or metallic stent placement[42-44]. Short-term outcome of EUS-BD for a small number of these patients was promising, though no long-term data is available[8,11,14,18,21,27,31]. Anterograde balloon dilation has been reported in very few cases, with a successful short-term outcome[8,14,21], and transgastric placement of multiple plastic stents across the anastomotic stricture was feasible in select patients. One patient in our report had a good long-term result after three years[8]. Because of the repeated nature of the procedures in this group for the assessment of stricture patency or insertion of an additional stent, EUS-BD with anterograde or rendezvous techniques may be initially selected as a bridging procedure in the patients with endoscopic access of the papilla or biliary anastomotic site, but failed ERCP cannulation. At present, EUS-BD in patients with benign stricture and failed OAE-ERPC access to the papilla or biliary anastomosis is challenging. In patients with malignant strictures, the same approach is applicable, but transluminal drainage is preferred, as repeated procedures may be easier using a standard endoscope. In patients with bile duct stones associated with altered anatomy and OAE-ERCP access to the papilla or biliary anastomosis with failed ERCP cannulation, EUS-BD with anterograde or rendezvous procedures may be preferred for stone removal[4,45]. EUS-BD with anterograde stone removal using balloon dilation with the stones pushed across the ampulla or anastomosis was reported in 11 patients with one failure[8,14,22], and may be an option in select patients with failed OAE-ERCP access to the papilla or biliary anastomosis. Placement of a transgastric nasobiliary drainage tube or a plastic stent to maintain access for subsequent repeated procedures was also an option[8,14]. The details of the procedure should be customized based on clinical setting.

EUS-BD as an initial modality

OAE-ERCP is increasingly used in patients with altered anatomy with more supporting data compared with EUS-BD[4,8,11,14,18-32,45], though no comparative studies are available. In patients with benign strictures, standard ERCP (for patients with Billroth Ⅰ or Ⅱ anatomy, Whipple's operation,) or OAE-ERCP is more suitable because of the likelihood for repeated procedures for additional stent placement or stent exchange. In patients with malignant strictures, EUS-BD may be an alternative to PTBD in centers with appropriate expertise when OAE-ERCP is not available, however, this should be done in a research setting. For patients with bile duct stones, OAE-ERCP may be suitable as the options for treatment of the stones are more readily available, and EUS-BD should be reserved for patients in whom this procedure fails.

Limitations of EUS-BD

As it is difficult to pass the linear EUS endoscope into the afferent limb[46], EUS-CDS is not the appropriate option for patients with altered anatomies. The EUS-BD drainage access is limited to the left biliary system, and requires the presence of a dilated ductal system. Manipulation of the guide-wire to cross a stricture or papilla may be difficult, and the guide-wire can be sheared[47,48]. As only limited data for anterograde EUS-BD were available[48], the success rate may be lower with a lower complication rate compared with other techniques[7]. EUS-hepaticogastrostomy is limited by the lack of adherence between the stomach and the liver, which may increase the risk of stent dislocation and lead to bile leak. The risk of bleeding from the liver may also increase[48]. The main limitation of the rendezvous method is the requirement of an endoscopically accessible papilla or anastomosis, which is always troublesome in cases of surgically altered anatomy. In addition, the rendezvous procedure requires exchanging the echoendoscope for a duodenoscope, during which guide-wire access can be lost[48].

The majority of the data concerning EUS-BD is reported by experts, and may not translate to clinical practice. For example, in a national study in Spain involving community endoscopists, EUS-BD had a lower success rate (67.2%) and a complication rate of 23.2%[15]. Moreover, there is no well-designed EUS-training system and training using swine models, or computer-based simulators are expensive and not accessible by all trainees[47]. This may hinder the establishment of skills in therapeutic EUS.

FUTURE DEVELOPMENTS

Most of EUS-BDs were performed with conventional fine-needle aspiration needles. The new 19-gauge blunt tip (Echo-HD; Cook Medical, Bloomington, IN, United States) may reduce catching at the needle tip during to-and-fro manipulation of a guide-wire that may reduce shearing. Needle-knife dilation was reported to increase the risk of complications in EUS-BD[49]. The tip of the needle knife may not align with the axis of the guide-wire, thus a 6 Fr catheter with diathermic ring (Endoflex, Voerde, Germany) was used in some centers[47]. A prototype compression coil and twin-headed needle may simplify the EUS-BD procedure, and shows promise for use in EUS-CDS in a study in canines[50]. The development of a forward-viewing echoendoscope allows simultaneous visualization of the endoscopic and EUS operating fields, while the perpendicular access and lack of angulation at the exit of the working channel allow for easy introduction of a 19-gauge needle and passing of the stent without indentation[51]. Although the forward-viewing echoendoscope showed a high success rate for EUS-CDS in a prospective case series[52], further studies are needed to confirm its advantage in EUS-BD. Multiple exchanges over the wire during EUS-BD may increase the risk of leakage, increase the procedure time, and increase the chance to lose guide-wire access[47]. Non-exchange systems have been evaluated in experimental animal studies[53,54], and may minimize the aforementioned drawbacks of the current EUS-BD technique when the devices are available in the future.

CONCLUSION

EUS-guided biliary intervention is technically feasible and the available data indicate a high success rate in patients with surgically altered anatomies. Although the complication rate may be higher than for OAE-ERCP in patients with altered anatomy (17.5% *vs* 3.4%[4]), EUS-BD may be a rescue option in patients for whom OAE-ERCP has failed when conducted within centers with appropriate expertise and in a research setting. A standardized algorithm for using different EUS-BD techniques, refinement of these methods, and the development of new devices may improve the efficacy of EUS-BD and minimize the complication rate. The role of forward-viewing echoendoscope and comparison with the current standard EUS endoscope remain to be assessed.

COMMENTS

Background

Surgically altered anatomy is a consequence of an operation for treatment of a specific disease. This precludes a normal access to the bile duct opening by a standard duodenoscope in many cases and an over-tube assisted endoscopy (OAE) is usually needed to access the bile duct. However, OAE has a failure rate as high as 26%. Endoscopic ultrasound guided biliary drainage (EUS-BD), a recently developed technique, showed a high success rate. The efficacy of EUS-BD in altered anatomy is not well defined.

Research frontiers

To the best of our knowledge, no review of EUS-BD in surgically altered anatomy has been previously published. The objective of this study was to review systematically the efficacy of EUS-BD in altered anatomy.

Innovations and breakthroughs

EUS-BD in the setting of surgically altered anatomy has an efficacy similar to EUS-BD in general, nonetheless, the available data were limited and further studies to evaluate the role of EUS-BD in altered anatomy are needed.

Applications

EUS-BD may be an option for patient with surgically altered anatomy with a failed OAE therapeutic intervention but this should be done in centers with the expertise in EUS-BD in a research setting.

Terminology

EUS-BD is a technique using an endoscope with ultrasound technology to visualize a bile duct. A needle puncture of the bile duct was done under ultrasound guidance then intervention was done using various kinds of endoscopic accessories. OAE is a technique of endoscopy that utilizing an over-tube with a balloon at the tip or an over-tube with a spiral configuration to facilitate the insertion of an enteroscope.

Peer-review

This study was well investigated and will give us important information especially in clinical gastroenterology.

REFERENCES

1 **Freeman ML**, Guda NM. ERCP cannulation: a review of reported techniques. *Gastrointest Endosc* 2005; **61**: 112-125 [PMID: 15672074 DOI: 10.1016/S0016-5107(04)02463-0]

2 **Hintze RE**, Veltzke W, Adler A, Abou-Rebyeh H. Endoscopic sphincterotomy using an S-shaped sphincterotome in patients with a Billroth II or Roux-en-Y gastrojejunostomy. *Endoscopy* 1997; **29**: 74-78 [PMID: 9101142 DOI: 10.1055/s-2007-1004078]

3 **Wright BE**, Cass OW, Freeman ML. ERCP in patients with long-limb Roux-en-Y gastrojejunostomy and intact papilla. *Gastrointest Endosc* 2002; **56**: 225-232 [PMID: 12145601]

4 **Skinner M**, Popa D, Neumann H, Wilcox CM, Mönkemüller K. ERCP with the overtube-assisted enteroscopy technique: a systematic review. *Endoscopy* 2014; **46**: 560-572 [PMID: 24839188 DOI: 10.1055/s-0034-1365698]

5 **Kühn JP**, Busemann A, Lerch MM, Heidecke CD, Hosten N, Puls R. Percutaneous biliary drainage in patients with nondilated intrahepatic bile ducts compared with patients with dilated intrahepatic bile ducts. *AJR Am J Roentgenol* 2010; **195**: 851-857 [PMID: 20858809 DOI: 10.2214/AJR.09.3461]

6 **Giovannini M**, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy* 2001; **33**: 898-900 [PMID: 11571690 DOI: 10.1055/s-2001-17324]

7 **Iwashita T**, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. *Clin J Gastroenterol* 2014; **7**: 94-102 [PMID: 24765215 DOI: 10.1007/s12328-014-0467-5]

8 **Attasaranya S**, Netinasunton N, Jongboonyanuparp T, Sottisuporn J, Witeerungrot T, Pirathvisuth T, Ovartlarnporn B. The Spectrum of

Endoscopic Ultrasound Intervention in Biliary Diseases: A Single Center's Experience in 31 Cases. *Gastroenterol Res Pract* 2012; **2012**: 680753 [PMID: 22654900 DOI: 10.1155/2012/680753]
9 **Sarkaria S**, Lee HS, Gaidhane M, Kahaleh M. Advances in endoscopic ultrasound-guided biliary drainage: a comprehensive review. *Gut Liver* 2013; **7**: 129-136 [PMID: 23560147 DOI: 10.5009/gnl.2013.7.2.129]
10 **Kedia P**, Gaidhane M, Kahaleh M. Endoscopic guided biliary drainage: how can we achieve efficient biliary drainage? *Clin Endosc* 2013; **46**: 543-551 [PMID: 24143319 DOI: 10.5946/ce.2013.46.5.543]
11 **Kahaleh M**, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. *Gastrointest Endosc* 2006; **64**: 52-59 [PMID: 16813803 DOI: 10.1016/j.gie.2006.01.063]
12 **Maranki J**, Hernandez AJ, Arslan B, Jaffan AA, Angle JF, Shami VM, Kahaleh M. Interventional endoscopic ultrasound-guided cholangiography: long-term experience of an emerging alternative to percutaneous transhepatic cholangiography. *Endoscopy* 2009; **41**: 532-538 [PMID: 19533558 DOI: 10.1055/s-0029-1214712]
13 **Kahaleh M**, Wang P, Shami VM, Tokar J, Yeaton P. EUS-guided transhepatic cholangiography: report of 6 cases. *Gastrointest Endosc* 2005; **61**: 307-313 [PMID: 15729253 DOI: 10.1016/S0016-5107(04)02585-4]
14 **Iwashita T**, Yasuda I, Doi S, Uemura S, Mabuchi M, Okuno M, Mukai T, Itoi T, Moriwaki H. Endoscopic ultrasound-guided antegrade treatments for biliary disorders in patients with surgically altered anatomy. *Dig Dis Sci* 2013; **58**: 2417-2422 [PMID: 23535877 DOI: 10.1007/s10620-013-2645-6]
15 **Vila JJ**, Pérez-Miranda M, Vazquez-Sequeiros E, Abadia MA, Pérez-Millán A, González-Huix F, Gornals J, Iglesias-Garcia J, De la Serna C, Aparicio JR, Subtil JC, Alvarez A, de la Morena F, García-Cano J, Casi MA, Lancho A, Barturen A, Rodríguez-Gómez SJ, Repiso A, Juzgado D, Igea F, Fernandez-Urien I, González-Martin JA, Armengol-Miró JR. Initial experience with EUS-guided cholangiopancreatography for biliary and pancreatic duct drainage: a Spanish national survey. *Gastrointest Endosc* 2012; **76**: 1133-1141 [PMID: 23021167 DOI: 10.1016/j.gie.2012.08.001]
16 **Iwashita T**, Lee JG, Shinoura S, Nakai Y, Park DH, Muthusamy VR, Chang KJ. Endoscopic ultrasound-guided rendezvous for biliary access after failed cannulation. *Endoscopy* 2012; **44**: 60-65 [PMID: 22127960 DOI: 10.1055/s-0030-1256871]
17 **Khashab MA**, Valeshabad AK, Modayil R, Widmer J, Saxena P, Idrees M, Iqbal S, Kalloo AN, Stavropoulos SN. EUS-guided biliary drainage by using a standardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques (with videos). *Gastrointest Endosc* 2013; **78**: 734-741 [PMID: 23886353 DOI: 10.1016/j.gie.2013.05.013]
18 **Artifon EL**, Safatle-Ribeiro AV, Ferreira FC, Poli-de-Figueiredo L, Rasslan S, Carnevale F, Otoch JP, Sakai P, Kahaleh M. EUS-guided antegrade transhepatic placement of a self-expandable metal stent in hepatico-jejunal anastomosis. *JOP* 2011; **12**: 610-613 [PMID: 22072253]
19 **Ogura T**, Masuda D, Imoto A, Takeushi T, Kamiyama R, Mohamed M, Umegaki E, Higuchi K. EUS-guided hepaticogastrostomy combined with fine-gauge antegrade stenting: a pilot study. *Endoscopy* 2014; **46**: 416-421 [PMID: 24573771 DOI: 10.1055/s-0034-1365020]
20 **Nguyen-Tang T**, Binmoeller KF, Sanchez-Yague A, Shah JN. Endoscopic ultrasound (EUS)-guided transhepatic anterograde self-expandable metal stent (SEMS) placement across malignant biliary obstruction. *Endoscopy* 2010; **42**: 232-236 [PMID: 20119894 DOI: 10.1055/s-0029-1243858]
21 **Park do H**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided transhepatic antegrade balloon dilation for benign bilioenteric anastomotic strictures in a patient with hepaticojejunostomy. *Gastrointest Endosc* 2012; **75**: 692-693 [PMID: 21679943 DOI: 10.1016/j.gie.2011.04.013]
22 **Weilert F**, Binmoeller KF, Marson F, Bhat Y, Shah JN. Endoscopic ultrasound-guided anterograde treatment of biliary stones following gastric bypass. *Endoscopy* 2011; **43**: 1105-1108 [PMID: 22057823 DOI: 10.1055/s-0030-1256961]
23 **Prachayakul V**, Aswakul P. A novel technique for endoscopic ultrasound-guided biliary drainage. *World J Gastroenterol* 2013; **19**: 4758-4763 [PMID: 23922474 DOI: 10.3748/wjg.v19.i29.4758]
24 **Shah JN**, Marson F, Weilert F, Bhat YM, Nguyen-Tang T, Shaw RE, Binmoeller KF. Single-operator, single-session EUS-guided anterograde cholangiopancreatography in failed ERCP or inaccessible papilla. *Gastrointest Endosc* 2012; **75**: 56-64 [PMID: 22018554 DOI: 10.1016/j.gie.2011.08.032]
25 **Püspök A**, Lomoschitz F, Dejaco C, Hejna M, Sautner T, Gangl A. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. *Am J Gastroenterol* 2005; **100**: 1743-1747 [PMID: 16086710 DOI: 10.1111/j.1572-0241.2005.41806.x]
26 **Park do H**, Jeong SU, Lee BU, Lee SS, Seo DW, Lee SK, Kim MH. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). *Gastrointest Endosc* 2013; **78**: 91-101 [PMID: 23523301 DOI: 10.1016/j.gie.2013.01.042]
27 **Bories E**, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. *Endoscopy* 2007; **39**: 287-291 [PMID: 17357952 DOI: 10.1055/s-2007-966212]
28 **Ma J**, Liu Y, Li Z, Jin Z. Endoscopic ultrasound-guided transgastric biliary drainage after partial gastrectomy. *Endoscopy* 2011; **43** Suppl 2 UCTN: E102 [PMID: 21424995 DOI: 10.1055/s-0030-1256104]
29 **Kawakubo K**, Isayama H, Kato H, Itoi T, Kawakami H, Hanada K, Ishiwatari H, Yasuda I, Kawamoto H, Itokawa F, Kuwatani M, Iiboshi T, Hayashi T, Doi S, Nakai Y. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. *J Hepatobiliary Pancreat Sci* 2014; **21**: 328-334 [PMID: 24026963 DOI: 10.1002/jhbp.27]
30 **Horaguchi J**, Fujita N, Noda Y, Kobayashi G, Ito K, Obana T, Takasawa O, Koshita S, Kanno Y. Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage. *Dig Endosc* 2009; **21**: 239-244 [PMID: 19961522 DOI: 10.1111/j.1443-1661.2009.00899.x]
31 **Will U**, Thieme A, Fueldner F, Gerlach R, Wanzar I, Meyer F. Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage. *Endoscopy* 2007; **39**: 292-295 [PMID: 17357950 DOI: 10.1055/s-2007-966215]
32 **Burmester E**, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: report of 4 cases. *Gastrointest Endosc* 2003; **57**: 246-251 [PMID: 12556796 DOI: 10.1067/mge.2003.85]
33 **Kamiya S**, Nagino M, Kanazawa H, Komatsu S, Mayumi T, Takagi K, Asahara T, Nomoto K, Tanaka R, Nimura Y. The value of bile replacement during external biliary drainage: an analysis of intestinal permeability, integrity, and microflora. *Ann Surg* 2004; **239**: 510-517 [PMID: 15024312 DOI: 10.1097/01.sla.0000118594.23874.89]
34 **Khashab MA**, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, Saxena P, El Zein M, Lennon AM, Canto MI, Kalloo AN. A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP. *Dig Dis Sci* 2015; **60**: 557-565 [PMID: 25081224 DOI: 10.1007/s10620-014-3300-6]
35 **Bapaye A**, Dubale N, Aher A. Comparison of endosonography-guided vs. percutaneous biliary stenting when papilla is inaccessible for ERCP. *United European Gastroenterol J* 2013; **1**: 285-293 [PMID: 24917973 DOI: 10.1177/2050640613490928]
36 **Artifon EL**, Aparicio D, Paione JB, Lo SK, Bordini A, Rabello C, Otoch JP, Gupta K. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. *J Clin Gastroenterol* 2012; **46**: 768-774 [PMID: 22810111 DOI: 10.1097/MCG.0b013e31825f264c]

37 **Imazu H**, Kanazawa K, Ikeda K, Kakutani H, Sumiyama K, Ang TL, Omar S, Tajiri H. Initial evaluation of a novel multibending backward-oblique viewing duodenoscope in endoscopic retrograde cholangiopancreatography. *Endoscopy* 2012; **44**: 99-102 [PMID: 22068702 DOI: 10.1055/s-0031-1291445]

38 **Schreiner MA**, Chang L, Gluck M, Irani S, Gan SI, Brandabur JJ, Thirlby R, Moonka R, Kozarek RA, Ross AS. Laparoscopy-assisted versus balloon enteroscopy-assisted ERCP in bariatric post-Roux-en-Y gastric bypass patients. *Gastrointest Endosc* 2012; **75**: 748-756 [PMID: 22301340 DOI: 10.1016/j.gie.2011.11.019]

39 **Lopes TL**, Clements RH, Wilcox CM. Laparoscopy-assisted ERCP: experience of a high-volume bariatric surgery center (with video). *Gastrointest Endosc* 2009; **70**: 1254-1259 [PMID: 19846085 DOI: 10.1016/j.gie.2009.07.035]

40 **Desai SV**, Naveed M, Jazwinski A, Jowell PS, Branch MS. Spiral enteroscopy versus laparoscopic-assisted endoscopy for completion of ERCP in patients with roux-en-y gastric bypass surgery [abstract]. *Gastrointest Endosc* 2011; **73**: AB122 [DOI: 10.1016/j.gie.2011.03.039]

41 **Bertin PM**, Singh K, Arregui ME. Laparoscopic transgastric endoscopic retrograde cholangiopancreatography (ERCP) after gastric bypass: case series and a description of technique. *Surg Endosc* 2011; **25**: 2592-2596 [PMID: 21416184 DOI: 10.1007/s00464-011-1593-5]

42 **Devière J**, Nageshwar Reddy D, Püspök A, Ponchon T, Bruno MJ, Bourke MJ, Neuhaus H, Roy A, González-Huix Lladó F, Barkun AN, Kortan PP, Navarrete C, Peetermans J, Blero D, Lakhtakia S, Dolak W, Lepilliez V, Poley JW, Tringali A, Costamagna G. Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology* 2014; **147**: 385-395; quiz e15 [PMID: 24801350 DOI: 10.1053/j.gastro.2014.04.043]

43 **Baron TH**, Davee T. Endoscopic management of benign bile duct strictures. *Gastrointest Endosc Clin N Am* 2013; **23**: 295-311 [PMID: 23540962 DOI: 10.1016/j.giec.2013.01.001]

44 **Costamagna G**, Boškoski I. Current treatment of benign biliary strictures. *Ann Gastroenterol* 2013; **26**: 37-40 [PMID: 24714594]

45 **Shah RJ**, Smolkin M, Yen R, Ross A, Kozarek RA, Howell DA, Bakis G, Jonnalagadda SS, Al-Lehibi AA, Hardy A, Morgan DR, Sethi A, Stevens PD, Akerman PA, Thakkar SJ, Brauer BC. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). *Gastrointest Endosc* 2013; **77**: 593-600 [PMID: 23290720 DOI: 10.1016/j.gie.2012.10.015]

46 **Wilson JA**, Hoffman B, Hawes RH, Romagnuolo J. EUS in patients with surgically altered upper GI anatomy. *Gastrointest Endosc* 2010; **72**: 947-953 [PMID: 21034896 DOI: 10.1016/j.gie.2010.07.016]

47 **Kahaleh M**, Artifon EL, Perez-Miranda M, Gupta K, Itoi T, Binmoeller KF, Giovannini M. Endoscopic ultrasonography guided biliary drainage: summary of consortium meeting, May 7th, 2011, Chicago. *World J Gastroenterol* 2013; **19**: 1372-1379 [PMID: 23538784 DOI: 10.3748/wjg.v19.i9.1372]

48 **Binmoeller KF**, Nguyen-Tang T. Endoscopic ultrasound-guided anterograde cholangiopancreatography. *J Hepatobiliary Pancreat Sci* 2011; **18**: 319-331 [PMID: 21190119 DOI: 10.1007/s00534-010-0358-1]

49 **Park do H**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc* 2011; **74**: 1276-1284 [PMID: 21963067 DOI: 10.1016/j.gie.2011.07.054]

50 **Chang KJ**, Chao HH. EUS-Guided choledocho-duodenostomy (ECD) for immediate and long-term treatment of biliary obstruction using prototype compression coil and twin-head needle. *Gastrointest Endosc* 2011; **73**: AB326

51 **Fusaroli P**, Ceroni L, Caletti G. Forward-view Endoscopic Ultrasound: A Systematic Review of Diagnostic and Therapeutic Applications. *Endosc Ultrasound* 2013; **2**: 64-70 [PMID: 24949367 DOI: 10.4103/2303-9027.117689]

52 **Hara K**, Yamao K, Hijioka S, Mizuno N, Imaoka H, Tajika M, Kondo S, Tanaka T, Haba S, Takeshi O, Nagashio Y, Obayashi T, Shinagawa A, Bhatia V, Shimizu Y, Goto H, Niwa Y. Prospective clinical study of endoscopic ultrasound-guided choledochoduodenostomy with direct metallic stent placement using a forward-viewing echoendoscope. *Endoscopy* 2013; **45**: 392-396 [PMID: 23338620 DOI: 10.1055/s-0032-1326076]

53 **Binmoeller KF**, De La Mora-Levy JG. An Exchange-Free Device for Advanced Translumenal Therapy. *Gastrointest Endosc* 2010; **71**: AB349

54 **Lee TH**, Choi JH, Lee SS, Cho HD, Seo DW, Park SH, Lee SK, Kim MH, Park do H. A pilot proof-of-concept study of a modified device for one-step endoscopic ultrasound-guided biliary drainage in a new experimental biliary dilatation animal model. *World J Gastroenterol* 2014; **20**: 5859-5866 [PMID: 24914346 DOI: 10.3748/wjg.v20.i19.5859]

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CASE REPORT

Esophageal papilloma: Flexible endoscopic ablation by radiofrequency

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

Squamous papilloma of the esophagus is a rare benign lesion of the esophagus. Radiofrequency ablation is an established endoscopic technique for the eradication of Barrett esophagus. No cases of endoscopic ablation of esophageal papilloma by radiofrequency ablation (RFA) have been reported. We report a case of esophageal papilloma successfully treated with a single session of radiofrequency ablation. Endoscopic ablation of the lesion was achieved by radiofrequency using a new catheter inserted through the working channel of endoscope. The esophageal ablated tissue was removed by a specifically designed cup. Complete ablation was confirmed at 3 mo by endoscopy with biopsies. This case supports feasibility and safety of as a new potential indication for Barrx™ RFA in patients with esophageal papilloma.

Key words: Esophageal papilloma; Endoscopic ablation; Radiofrequency; Minimally invasive; Natural orifice transluminal endoscopic surgery

Core tip: This paper reports for the first time a flexible endoscopic treatment of esophageal papilloma by a new radiofrequency system that goes into the working channel of the endoscope. This allows the endoscopist to see what he is doing along the procedure and to complete the procedure in few minutes. The procedure was performed without particular difficulties and did not required elevated skills.

del Genio G, del Genio F, Schettino P, Limongelli P, Tolone S, Brusciano L, Avellino M, Vitiello C, Docimo G, Pezzullo

A, Docimo L. Esophageal papilloma: Flexible endoscopic ablation by radiofrequency. *World J Gastrointest Endosc* 2015; 7(3): 290-294 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i3/290.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i3.290

INTRODUCTION

Esophageal benign lesion is often a major concern due to need of an effective and low risk procedure combined to unmodified physiology[1]. Radiofrequency ablation (RFA) is an established endoscopic technique for the eradication of Barrett esophagus, which has been investigated in a variety of study designs and settings[2-6].

RFA is associated with an acceptable safety profile, high rates of complete eradication of dysplasia and intestinal metaplasia, durability of effect, and a significant relative risk reduction for neoplastic progression, thus it is considered a standard of care for patients with high-grade dysplasia[7].

Squamous papilloma (SP) of the esophagus is a rare benign lesion of the esophagus. The prevalence ranges from 0.01% to 0.45%[8]. SP of the esophagus is usually asymptomatic and rarely causes dysphagia. Esophageal squamous papillomatosis is typically reported as a wart-like and fleshy-pink single lesion, most commonly in the middle or distal esophagus; the typical endoscopic appearance is a single, round sessile lesion[9]. The underlying etiology is unclear, but chronic reflux disease, mucosal trauma, and human papillomavirus (HPV) infection have been implicated, although most lesions are found in absence of HPV[10]. The malignant potential of the lesion is unknown, and no guidelines exist regarding follow-up of these lesions[11]. Some authors have recently reported the possibility of an endoscopic removal[12,13]. To the best of our knowledge, no cases of endoscopic ablation of esophageal papilloma by RFA has been reported. We report a case of esophageal papilloma successfully treated with a single session of RFA.

CASE REPORT

This case was conducted according to the Declaration of Helsinki and approved by the local institutional review board. In February 2014, a 52-year-old white asymptomatic woman was referred to our unit in the preoperative assessment of intragastric baloon placement for obesity. Upper gastrointestinal endoscopy (UGIE) revealed the presence of a single whitish wart-like area of about 0.5 cm in diameter which was located 37 cm from the incisors, above the Z-line (Figure 1). Narrow band imaging (NBI) confirmed the presence of an unstained area. Histologic examination showed the presence of micropapilloma of the esophagus surrounded by cilindric epithelium with congestion and flogosis (Figure 2). In April 2014 a session of RFA (Barrx™, Covidien, CA, United States) on the dysmorphic esophageal area was performed. Total length of the procedure was 10 min. No complications occurred during the procedure. Postoperative course was uneventful.

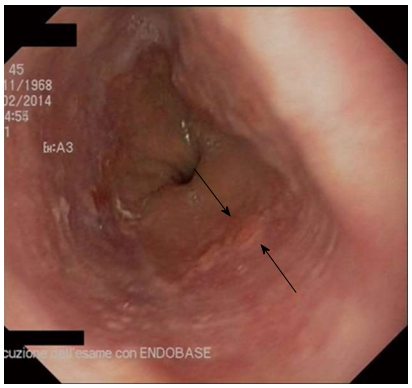

Figure 1 Endoscopic view of esophageal papilloma.

Endoscopic technique

The patient was positioned in the left lateral decubitus position under monitoring of vital signs. Intravenous sedation was administered. An UGIE allowed identification of the esophageal papilloma. The total length of the area was calculated. Esophageal lumen was pre-treated with N-acetycysteine 1% (Mucomyst™). A new designed catheter (Channel RFA Endoscopic Catheter, Barrx™, Covidien) was inserted through the working channel of a standard flexible gastroscope (Figure 3). The electric pad of the catheter was placed under direct visualization so that the entire suspected area was covered. Radiofrequency was applied at 300 W and 12 J/cm^2. The wound along the ablation zone was cleaned from debris using Barrx™ RFA Cleaning cup mounted on distal end of endoscope. The ablation was repeated using the same procedure (Figure 4). The patient was discharged the same day. An UGIE was repeated after one months, showing a whitish area suggestive of scarring at the site of ablation without macroscopical evidence of residual papilloma. A second UGIE with biopsies, at 3 mo, excluded the presence of recurrent disease.

DISCUSSION

RFA has been recently reported to be more effective and less costly than photodynamic therapy in the treatment of Barrett's related dysplasia[14]. On the other hand, an important advantage of RFA lays on simplicity and safety of the procedure suggesting the treatment can be effective with potential lower complications rates than more invasive techniques such as endoscopic resection. In this case an asymptomatic patient was discovered to have an esophageal papilloma in course of preoperative EGDS

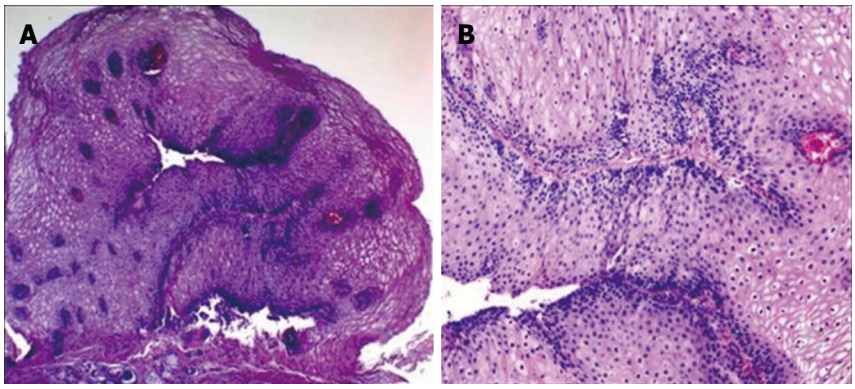

Figure 2 Esophageal biopsy showing papillary projections lined with acanthotic squamous epithelium (A: HE 4 ×; B: HE 10 ×).

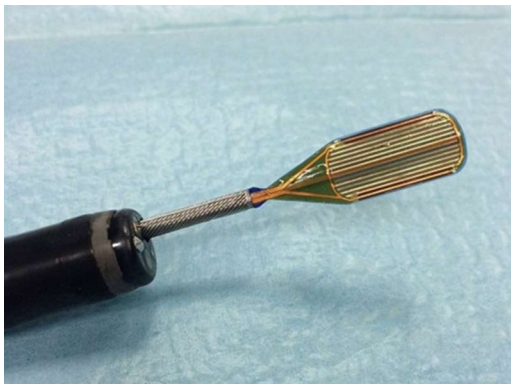

Figure 3 Radiofrequency catheter inserted into standard flexible gastroscope operative channel (Barrx™, Covidien).

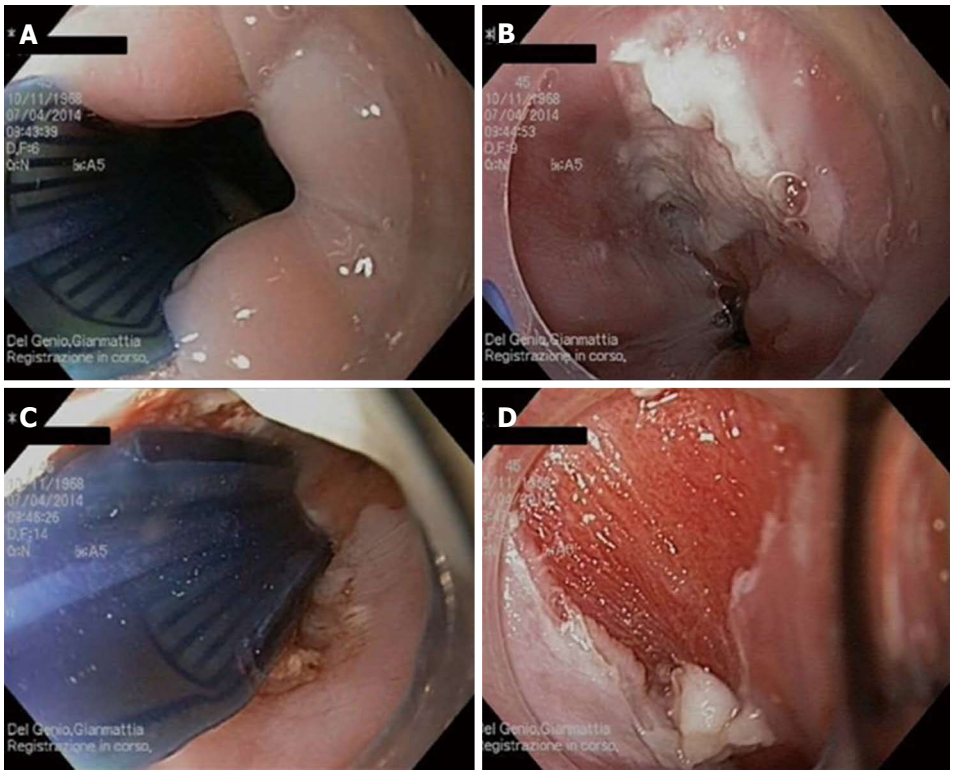

Figure 4 Radiofrequency pad is placed over the lesion under direct visualization (A); Ablation area after the first application of energy (B); Second application of the pad to include all the area of esophageal papilloma (C); Esophageal wound cleaned from debris by cleaning cup (D).

before bariatric treatment.

In this case, the efficacy was reached by a single session of RFA, with a minimal discomfort for the patient and a relatively low impact on the endoscopic center. Our initial experience supports the feasibility and safety of a new potential indication for Barrx™ RFA in patients with esophageal papilloma. Further cases and a longer follow up will be needed to drive a definitive conclusion.

ACKNOWLEDGMENTS

"Considerate la vostra semenza: Fatti non foste a viver come bruti, ma per seguir virtute e canoscenza." (Consider well the seed that gave you birth: you were not made to live as brutes, but to follow virtue and knowledge). Ulysses in The Divine Comedy. Dante Alighieri, Canto XXVI, 1308-21.

COMMENTS

Case characteristics

A 52-year-old female with esophageal papilloma.

Clinical diagnosis

The tumor was diagnosed during routine gastroscopy for preoperative assessment before placing intragastric baloon.

Differential diagnosis

Esophageal high grade dysplasia, metaplasia, early adenocarcimona or squamous cell carcinoma.

Laboratory diagnosis

All blood test were within normal limits.

Imaging diagnosis

Upper endoscopy showed the lesion, byopsies were taken.

Pathological diagnosis

Histologic examination showed the presence of micropapilloma of the esophagus surrounded by cilindric epithelium with congestion and flogosis.

Treatment

Single treatment of endoscopic ablation by radiofrequency.

Related reports

Endoscopic curative treatment is becoming more popular. This is the first report of squamous esophageal papilome treated by a new catheter radiofrequency technology.

Term explanation

RFA: Radiofrequency ablation is a relatively new technique generally used to treat Barrett's esophagus related high grade dysplasia. This technology uses bipolar energy associated to impedance to automatically controll the energy output.

Experiences and lessons

The new technical possibility allows a less invasive approach with a reduced risks of potentially serious complication and a faster return to normal life.

Peer-review

The manuscript is very well.

REFERENCES

1 **Del Genio G**, Tolone S, Del Genio F, D'Alessandro A, Brusciano L, Aggarwal R, Conzo G, Orditura M, Docimo L, Del Genio A. Impact of total fundoplication on esophageal transit: analysis by combined multichannel intraluminal impedance and manometry. *J Clin Gastroenterol* 2012; **46**: e1-e5 [PMID: 22157223 DOI: 10.1097/MCG.0b013e31822f3735]

2 **Phoa KN**, Pouw RE, van Vilsteren FG, Sondermeijer CM, Ten Kate FJ, Visser M, Meijer SL, van Berge Henegouwen MI, Weusten BL, Schoon EJ, Mallant-Hent RC, Bergman JJ. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. *Gastroenterology* 2013; **145**: 96-104 [PMID: 23542068 DOI: 10.1053/j.gastro.2013.03.046]

3 **van Vilsteren FG**, Pouw RE, Seewald S, Alvarez Herrero L, Sondermeijer CM, Visser M, Ten Kate FJ, Yu Kim Teng KC, Soehendra N, Rösch T, Weusten BL, Bergman JJ. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. *Gut* 2011; **60**: 765-773 [PMID: 21209124 DOI: 10.1136/gut.2010.229310]

4 **Pouw RE**, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, Devière J, Neuhaus H, Bergman JJ. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol* 2010; **8**: 23-29 [PMID: 19602454 DOI: 10.1016/j.cgh.2009.07.003]

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

6 **Fleischer DE**, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R, Chang KJ, Muthasamy R, Lightdale CJ, Santiago N, Pleskow DK, Dean PJ, Wang KK. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* 2010; **42**: 781-789 [PMID: 20857372 DOI: 10.1055/s-0030-1255779]

7 **Phoa KN**, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, Fullarton G, Di Pietro M, Ravi N, Visser M, Offerhaus GJ, Seldenrijk CA, Meijer SL, ten Kate FJ, Tijssen JG, Bergman JJ. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA* 2014; **311**: 1209-1217 [PMID: 24668102 DOI: 10.1001/jama.2014.2511]

8 **Takeshita K**, Murata S, Mitsufuji S, Wakabayashi N, Kataoka K, Tsuchihashi Y, Okanoue T. Clinicopathological characteristics of esophageal squamous papillomas in Japanese patients--with comparison of findings from Western countries. *Acta Histochem Cytochem* 2006; **39**: 23-30 [PMID: 17460769]

9 **Lewin KJ**, Appelman HD. Tumors of the esophagus & stomach: atlas of tumor pathology. 3rd Series, Vol. 18. American Registry of Pathology. Washington, DC: Armed forced Institute of Pathology, 1995: 31-32

10 **Del Genio G**, Tolone S, Limongelli P, Brusciano L, D'Alessandro A, Docimo G, Rossetti G, Silecchia G, Iannelli A, del Genio A, del Genio F, Docimo L. Sleeve gastrectomy and development of "de novo" gastroesophageal reflux. *Obes Surg* 2014; **24**: 71-77 [PMID: 24249251 DOI: 10.1007/s11695-013-1046-4.]

11 **Odze R**, Antonioli D, Shocket D, Noble-Topham S, Goldman H, Upton M. Esophageal squamous papillomas. A clinicopathologic study of 38 lesions and analysis for human papillomavirus by the polymerase chain reaction. *Am J Surg Pathol* 1993; **17**: 803-812 [PMID: 8393303]

12 **Kim E**, Byrne MF, Donnellan F. Endoscopic mucosal resection of esophageal squamous papillomatosis. *Can J Gastroenterol* 2012; **26**: 780-781 [PMID: 23166898]

13 **del Genio G**, Rossetti G, Brusciano L, Limongelli P, Pizza F, Tolone S, Fei L, Maffettone V, Napolitano V, del Genio A. Laparoscopic Nissen-Rossetti fundoplication with routine use of

intraoperative endoscopy and manometry: technical aspects of a standardized technique. *World J Surg* 2007; **31**: 1099-1106 [PMID: 17426906]

14 **Ertan A**, Zaheer I, Correa AM, Thosani N, Blackmon SH. Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: efficacy, safety and cost-comparison. *World J Gastroenterol* 2013; **19**: 7106-7113 [PMID: 24222954 DOI: 10.3748/wjg.v19.i41.7106]

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