

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2021 August 16; 13(8): 238-355



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The primary aim of *World Journal of Gastrointestinal Endoscopy* (WJGE, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The WJGE is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for WJGE as 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; Production Department Director: *Yun-Jie Ma*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

LAUNCH DATE

October 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5190/editorialboard.htm>

PUBLICATION DATE

August 16, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Six intragastric balloons: Which to choose?

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Author contributions: Stavrou G performed the literature review, drafted and critically revised the manuscript; Shrewsbury AD performed language editing, drafted and critically revised the manuscript; Kotzampassi K conceived the original idea, performed the literature review, drafted and critically revised the manuscript; all authors have read and approve the final manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest for this article

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Manuscript source: Invited

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Abstract

Endoscopically placed intragastric balloons (IGBs) have played a significant role in obesity treatment over the last 30 years, successfully bridging the gap between lifestyle modification/pharmacotherapy and bariatric surgery. Since they provide a continuous sensation of satiety that helps the ingestion of smaller portions of food, facilitating maintenance of a low-calorie diet, they have generally been considered an effective and reversible, less invasive, non-surgical procedure for weight loss. However, some studies indicate that balloons have limited sustainable effectiveness for the vast majority attempting such therapy, resulting in a return to the previous weight after balloon removal. In this review we try to summarize the pros and cons of various balloon types, to guide decision making for both the physician and the obese individual looking for effective treatment. We analyzed the six most commonly used IGBs, namely the liquid-filled balloons Orbera, Spatz3, ReShape Duo and Elipse, and the gas-filled Heliosphere and Obalon - also including comments on the adjustable Spatz3, and the swallowable Obalon and Elipse - to optimize the choice for maximum efficacy and safety.

Key Words: Obesity; Intragastric balloon; Fluid-filled balloons; Gas-filled balloons; Swallowable balloons

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Core Tip: Intragastric balloons have played a significant role in the management of obesity. Their easy application, reversibility and good short-term results have led to the development of a wide variety of balloon types. However, long-term results are not as good, and concerns about complications have also arisen. We tried to analyze the characteristics and effectiveness of the 6 most popular balloon types, in order to

manuscript

Specialty type: Surgery

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: March 10, 2021

Peer-review started: March 10, 2021

First decision: May 5, 2021

Revised: May 17, 2021

Accepted: July 13, 2021

Article in press: July 13, 2021

Published online: August 16, 2021

P-Reviewer: Rabago LR, Romano L

S-Editor: Zhang H

L-Editor: A

P-Editor: Wang LYT


provide guidance in choosing the most appropriate balloon for each patient.

Citation: Stavrou G, Shrewsbury A, Kotzampassi K. Six intragastric balloons: Which to choose? *World J Gastrointest Endosc* 2021; 13(8): 238-259

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/238.htm>
DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.238>

INTRODUCTION

Obesity, defined as an excess of body weight, and particularly of body fat, and associated with an increased number of co-morbidities, remains a considerable threat to human health, due to the high prevalence of morbidity and mortality, both from the syndrome itself and the related co-morbidities. Lifestyle modification, covering the combination of energy restriction, physical exercise, and behavioral changes is widely recommended as a stepwise approach to control/treat obesity. However, this measure usually leads to a modest decrease in weight, with a short success time - somewhat similar results to that of pharmacotherapy[1-8].

Although the pathophysiology of obesity is complex, the excess in calorie intake lies at the root of the weight gain mechanism[9]. One of the factors associated with greater calorie intake is definitely the greater fasting gastric capacity[10]; thus, an obvious solution would be the reduction of gastric capacity: either by surgery (resection or bypass procedures) or by placing a space-occupying device, mimicking a bezoar[11].

Bariatric surgery is generally effective, but always carries the risk of complications as well as low patient acceptance. It is estimated that less than 1% of obese patients who qualify for bariatric surgery opt for this procedure, mainly for fear of perceived risks of postoperative complications and mortality and, among others, the high surgical costs, and the lack of access to surgery. Furthermore, surgery is not indicated for overweight and obese class I patients[12-17].

Therefore, endoscopic bariatric and metabolic therapies have emerged over the years, to provide less invasive options beyond lifestyle modifications, pharmacotherapy and surgery, for patients who have failed with conservative treatment and are not or not yet surgical candidates, or refuse surgery because of its invasiveness and fear of complications[12,18]. According to the Statements after the Brazilian Intragastric Balloon Consensus, held in Sao Paulo, Brazil, in June 2016, obese individuals who are candidates for balloon implantation must be over 12 years of age, with established puberty, while there is no maximum age limit, each patient being evaluated individually. The minimum body mass index (BMI) is 25 kg/m², after failure of clinical treatment, with no influence of BMI on the choice of balloon type, this being at the discretion of the physician. It is common sense that the presence of an active gastric ulcer, or in any other location, of gastric or esophageal varices, of a hiatal hernia longer than 5 cm as well as previous gastric surgery, are all considered as absolute contraindications[19]. Intragastric balloons (IGBs)-based on the philosophy of restrictive surgical procedures - are space-occupying devices, first described by Niebe in 1982[11]. They are the most extensively studied and the most commonly used endoscopic "therapies" for obesity, due to their great efficacy and safety. Five years later, in 1987, the consensus meeting of international experts in Tarpon Springs, Florida[20], defined a number of specifications for a balloon to be considered suitable for use and primarily safe: It must (1) have a smooth surface with low potential for causing erosions, ulcers or obstructions; (2) be constructed of durable materials that do not leak; (3) be filled with liquid and not air; (4) be marked with a radiopaque marker that allows proper follow up of the device in case of deflation; and (5) have the capability of being adjusted to various sizes.

Mathus-Vliegen *et al*[18] who have been studying their mode of action for more than a decade, considers IGBs to mediate satiety both peripherally, by being a physical impediment to food intake, by reducing the gastric capacity and by delaying gastric emptying, and centrally, by activating gastric stretch receptors that transmit signals *via* afferent vagal nerves, the solitary tract and paraventricular nuclei, to the ventromedial and lateral hypothalamus[21-23].

In the intervening decades these devices have evolved to become more functional, effective and safe and the whole procedure less invasive, while keeping the

advantages of being reversible and not altering the gastrointestinal anatomy[12,24,25].

Currently, there are many IGB designs, with little variation between them, several of which are now available in clinical practice, but few of which have gained Food and Drug Administration (FDA) approval. They may differ in relation to the method of insertion and removal, the filling volume, adjustability and duration of implantation, while still adhering to the main idea of the artificial bezoar that occupies space in the stomach causing mechanical gastric distention, and providing a continuous sensation of satiety, and thus reduction in food intake, finally resulting in weight loss[12,26,27].

In an effort to facilitate physician choice, the present study attempts to describe the technical characteristics of FDA and European Community (CE)-approved balloons, providing information on their effectiveness and safety, based on the large-scale clinical studies of the last decade.

BALLOON DESCRIPTION

Orbera IGB

Orbera IGB (Apollo Endosurgery, Austin, TX, United States), formerly BioEnterics IGB (BIB, Inamed Corporation, Santa Barbara, CA, United States) was the first of the new generation of balloons which appeared in 1991, following the Tarpon Springs Consensus meeting[20]. To date, it is the most popular and most commonly used endoscopic device for weight loss, having also the most historical data supporting its use; all the other balloons, which follow chronologically, are practically based on the same idea and, unavoidably are comparable to it[4,5,27-29].

The FDA-approved Orbera (2005) is a single spherical silicone-made balloon of about 13 cm in diameter, arriving commercially compressed and impacted at the end of a filling tube attached to a radiopaque self-sealing valve (Figure 1). After an initial diagnostic endoscopy, the balloon placement assembly is inserted orally into the gastric fundus and a volume of 500 to 700 mL saline solution - at the discretion of the physician - is used for balloon inflation through a closed infusion circuit, the whole procedure being performed under direct endoscopic supervision[13,30,31]. After completion of inflation, the infusion system is closed, creating a sudden vacuum resulting in the valve self-sealing and allowing the easy release of the filling tube, which is then gently pulled out through the mouth, leaving the balloon in the fundus, but floating freely in the stomach[32,33].

According to manufacturer, the Orbera balloon could safely remain implanted for up to a maximum of 6 mo, because of the increasing risk of perforation and sudden emptying thereafter, which might allow the balloon to migrate towards the gut and possibly obstruct the bowel[5,13]. It requires sedation and endoscopy for deflation and removal; a double-channel endoscope and two long-jaw rat-tooth forceps may facilitate the procedure[4,13].

For the last two years a balloon which can remain in situ for 12 mo has also been available; the second generation "Orbera365", having almost exactly the same characteristics[34].

Heliosphere balloon

Over the years, it has become obvious that the excess weight of a liquid-filled balloon is the cause of an increased rate of nausea, vomiting and epigastric pain in the days immediately following balloon placement; thus, the air-filled Heliosphere balloon, known as the Heliosphere bag (Helioscopie Medical implants, Vienne, France) was developed to circumvent this disadvantage, and was introduced into clinical practice in 2004[35,36].

It is a single spherical high-volume-capacity, air-filled, polyurethane balloon weighing less than 30 g and is enclosed in a silicone envelope. It requires endoscopy for positioning and is loaded with a simple inflation system, allowing 900-1000 mL of air, within a median time of 12 min[30,37-40]. The balloon is generally well-tolerated during the 6 mo implantation period. However, its use has raised several concerns about procedure-related complications due to technical difficulties in balloon passage through the cardia and the upper esophageal sphincter-large size, low pliability, high failure rates for positioning and spontaneous deflation[28,36,38]; similar difficulties have also been referred to during endoscopic removal, leading, in a few cases, to surgical removal or to the use of a rigid endoscope[35], thus, the use of a two-claw forceps for catching it in the valve is advised. The whole procedure generally takes longer than that for other balloons, including the Orbera, and results in more discomfort, making deep sedation a prerequisite for both patient and endoscopist[41].



Figure 1 Orbera balloon. (This photo is from our personal photo-archive).

A severe warning for those candidates for gas-filled-Heliosphere balloons is to totally refrain from scuba diving and travelling in unpressurized airplane cabins[5].

Spatz3® balloon

Spatz3® balloon (Spatz3; Spatz FGIA, Great Neck, NY, United States) is the 3rd generation Spatz device manufactured with the first criterion of the Tarpon Springs Conference requirements in mind -*i.e.*, its volume can be adjusted - increased or reduced - throughout the treatment period and not only initially at the time of inflation[20]. Additionally, it is the first balloon that can safely remain in the stomach for 360 d, thus facilitating sustained weight loss for one full year, as well as leaving more time for the patient to undergo feeding re-education and lifestyle modification. However, it has the serious disadvantage of not having a completely smooth surface, since the site for insertion of the filling valve forms a sort of 'tail'[42,43]. On the other hand, according to the manufactures, this 'tail' may prevent or delay a deflated balloon from passing through the duodenum. To date it has received the European Union CE mark but not yet gained FDA approval[42,44,45].

It is a spherical silicone, saline-filled balloon, with the unique feature of an extractable, thin, filling catheter with a valve at the end, which enables saline to be added or removed in situ, thus adjusting the intragastric volume according to patient tolerance and the desired weight-loss outcome. The system consists of 3 parts: the balloon; a silicone covered anchor, with an internal network, to facilitate balloon insertion and removal and prevent migration; and the silicone filling tube, able to stretch to modify the fluid volume of the balloon and shrink back into the stomach[35, 43,44] (Figure 2).

The Spatz3 is designed to be inserted with a well-lubricated endoscope. The balloon is mounted on the tip of the scope by the use of a type of 'condom'. After visual confirmation that the whole balloon and its apparatus is fully within the gastric cavity - so avoiding the risk of inflation within the esophagus - balloon inflation is carried out under direct view, with 400-700 mL of saline. After inflation, the filling catheter is pulled up until its valve reaches the patient's mouth. Then the catheter is disconnected from the valve, which is closed with its cap, which has a blue nylon loop. Holding the loop, the valve is gently pushed back towards the oropharynx and the gastroscope facilitates the correct positioning of the valve in the gastric fundus[45].

For balloon deflation, in the case of intolerance in the early days - excessive and/or persistent vomiting for more than 7 d - the blue nylon loop is grasped endoscopically by foreign body forceps and pulled up to the mouth. At this level the previous mentioned filling catheter is adjusted and, by aspiration of 100 to 300 mL, the balloon volume is appropriately reduced. The same process is followed, usually 3 mo after implantation when the patient stops or has minimized weight loss, or should he/she report a decrease in satiety, to increase the balloon volume by a standard volume of 250 mL[43,46]. At the end the 12-mo implantation period, the balloon must be



Figure 2 Spatz-3 balloon. [Courtesy of Ms Ariel Nezry (VP Marketing, Spatz FGIA Inc)].

removed endoscopically after emptying by standard balloon needle or deflation utilizing the valve, by the same process as for insertion. However, its size and the described irregular morphology make the endoscopic extraction more difficult and laborious, and thus anaesthesia is absolutely necessary[30,35,38,44].

ReShape Duo integrated dual balloon system

ReShape Duo integrated dual balloon system (ReShape Medical, Inc, San Clemente, CA, United States) consists of two independently filled silicone spheres joined by a central, short, non-communicating flexible silicone shaft. The main idea behind this system design is to decrease the chance of balloon intestinal migration should one of the balloons accidentally deflate. Additionally, this flexible configuration, according to the manufacturers, allows the balloons to conform to the natural contours of the stomach[5,30,47-49].

The ReShape Duo balloon, FDA-approved system is inserted transorally and advanced into the stomach by means of an endoscopic guidewire. Each is filled separately with up to 450 mL of saline (maximum total volume 900 mL), although a smaller volume is recommended for individuals less than 64.5 inches in height[47-51]. When inflated, it occupies a significant portion of the stomach (900 mL), while maintaining the natural gastric anatomy. For balloon system deflation and removal, after a maximum 6 mo period, anaesthesia and endoscopy are definitely required[5,49,52].

As of December 2018, Apollo Endosurgery (Apollo Endosurgery, Austin, TX, United States) purchased ReShape Medical and will focus exclusively on its own Orbera balloon going forward. With this transaction, the ReShape balloon will be phased out[53].

Obalon®

The Obalon® (Obalon Therapeutics Inc, Carlsbad, CA, United States) is a new thin-walled, 250 mL gas-filled, swallowable IGB, designed to allow easy gastric volume titration, by using additional balloons. It is an FDA-approved device, consisting of a series of three individual balloons, equating to a total volume of 750 mL that can be consequently swallowed one month apart, and is relatively well-tolerated by most patients[54].

Each balloon is compressed, folded, and fitted into a 6 g dissolvable gelatin capsule, which is swallowed under fluoroscopic visualization to verify that the entire capsule has entered the stomach[40,54,55]. A thin, 2 fr catheter is attached to the balloon and once the capsule reaches the stomach the other end of the catheter, which extends outside the mouth, is used for remote, automated balloon inflation to a maximal volume of 250 mL, using a canister filled with a proprietary air mixture that is mostly nitrogen based. The procedure is relatively easy and executable by a single operator. After balloon inflation, the catheter is detached and removed, allowing the balloon valve to safely self-seal[5,54-56].

The balloons can remain implanted for up to 6 mo and require endoscopy only for deflation and removal of all 3 balloons at the same time. The balloons are punctured and then grasped by forceps for extraction under general anaesthesia[40,54,56].

Recently, the FDA also approved the Obalon navigation system. It utilizes magnetic resonance to provide a real-time image of the Obalon on a computer screen instead of fluoroscopy to confirm balloon positioning. This technology, besides minimizing the exposure of patient and personnel to radiation and decreasing the cost of radiography, makes the procedure itself relatively easier. The Obalon has been used in pediatrics with promising results[54-56]. In Europe, the Obalon, rather than other balloons, is indicated for use for individuals with a lower BMI (27 kg/m²)[5].

Elipse balloon

The Elipse balloon (Elipse; Allurion Technologies, Wellesley, MA, United States) is a non-FDA-approved IGB, similar in size, shape and function to the most widely used and endoscopically placed Orbera balloon. However, this is the first intragastric device not requiring anaesthesia, or an invasive endoscopic procedure, either for placement or removal[36,57,58]. It thus represents an innovative option for weight loss, minimizing the costs and the complication risks of the endoscopic procedure for insertion or removal and hence offers an option to obese individuals feeling uncomfortable with endoscopy and/or at risk for anaesthesia[36,44]. However, by omitting the pre-implantation endoscopic surveillance of the stomach, the possibility of recognizing mucosal lesions (erosions or ulcers) or anatomical abnormalities (hiatus hernia), which could, theoretically, lead to unexpected complications at the time of balloon remaining in the stomach, is lost[57].

The balloon, made from a thin polymer film without rigid parts, is enclosed, well compressed, inside a small, swallowable vegetarian capsule attached to a thin catheter 75 cm long and 1.3 mm in diameter, *via* a self-sealing valve, and is designed to deploy spontaneously in the stomach. The capsule is as easily swollen with water as a pill, but in the case of difficulty, a stylet can be fed through the catheter to stiffen it, allowing the physician to gently push the capsule during swallowing. Once swallowed, its proper position in the stomach is confirmed through x-ray visualization of the balloon's radiopaque ring-shape marker; after which, the balloon is filled with 550 mL of fluid, consisting of distilled water with potassium sorbate preservative, through the catheter which is then removed by simply pulling it back[58-60]. Placement is performed in a 20 min outpatient visit.

After a 4 mo period, the device is designed to spontaneously empty; the reabsorbable material, remaining closed inside the sealing balloon valve, completely degrades, leaving the device to self - deflate and then naturally pass - thanks to its construction from a thin film without rigid parts-through the gastrointestinal tract and be excreted[35,36,46,57,58].

The ease of insertion and self-removal enables many physicians who do not perform endoscopy to use the balloon and this is expected to lower the total cost of diet programs. However, this may lead to its inappropriate implantation in unsuitable individuals and thus to increased risks of intolerance. Another cause of increased intolerance may be the absence of endoscopic surveillance of the stomach for any pathology prior to its insertion (Table 1).

EFFECTIVENESS FOR BODY WEIGHT LOSS

The first balloon fulfilling the Tarpon Springs Consensus standards was the Bioenterics IGB (Inamed® Corporation, Santa Barbara, CA, United States) now available as Orbera commercially available since 1991. For more than a decade it remained unique in the market, and thus, inevitably, is the subject of many observational and randomized published studies, analyzing its effectiveness, which, in most studies, was impressive. Today, almost 30 years later, the idea of using a balloon as a space-occupying device in the stomach to give the feeling of fullness, still remains not only attractive, but also effective, as demonstrated by the multiple attempts to copy, with modifications, the original idea, many of which have been considered successful and become commercially available. This chapter aims to show in numbers - through meta-analysis and large series - studies published in recent years - the effectiveness in weight loss of the IGBs now in use in clinical practice. For comparison and homogeneity of expression the parameters of percentage total body weight loss (%TBWL), percentage excess weight loss (%EWL) and BMI are used[51,61] (Table 2).

Table 1 Summary of Intra-gastric balloon characteristics

Balloon type	FDA/CE approved				CE approved	
	Orbera	ReShape Duo	Obalon	Heliosphere	Spatz	Elipse
Manufacturer	Apollo Endosurgery	ReShape Medical	Obalon Therapeutics	Helioscopia Medical Implants	Spatz FGIA	Allurion Technologies
Filled with	Saline	Saline	Nitrogen gas	Air	Saline	Liquid
Capacity (mL)	400-700	450 × 2	250 × 3	900-1000	300-900	550
Number of balloons	1	2	Up to 3	1	1	1
Insertion	Endoscopy	Endoscopy	Swallowed	Endoscopy	Endoscopy	Swallowed
Removal	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Natural pass
Duration	6	6	6	6	12	4
Adjustable	No	No	No	No	Yes	No

FDA: Food and Drug Administration; CE: European Community.

Table 2 Representative studies of the effectiveness of intra-gastric balloons

Ref.	Study type	Cases	Balloon type	Mo	Mean BMI loss kg/m ²	Mean BWL kg	%TWL	%EWL
Genco <i>et al</i> [64], 2005	Observational	2515	Bioenterics	6	4.9 ± 12.7			
Kotzampassi <i>et al</i> [13], 2012	Observational	500	Bioenterics	6	7.39 ± 3.57	21.19 ± 10.3		38.09 ± 20.18
Lopez-Nava <i>et al</i> [67], 2011	Observational	714	Bioenterics	6	6.5 ± 12.7	18.8 ± 9		41.6 ± 21.8
Fittipaldi-Fernandez <i>et al</i> [68], 2020	Observational	5874	air-filled	6		19.13 ± 8.86	18.42 ± 7.25	65.66 ± 36.24
Abu Dayyeh <i>et al</i> [71], 2019	Observational	187	Spatz3	9			14.9 ± 7.2 plus 4.7*	
Fittipaldi-Fernandez <i>et al</i> [45], 2020	Observational	180	Spatz3	7.12 ± 1.63	6.18 ± 4.07	17.51 ± 11.67	16.22 ± 9.74	56.68 ± 40.12
Schwaab <i>et al</i> [72], 2020	Cross-sectional	360/144	Orbera/Spatz3	6 up to 12			15.4 ± 7/15.5 ± 9.6	
Sullivan <i>et al</i> [73], 2018	RCT	185/181	Obalon/sham	6			6.6 ± 5.1/3.4 ± 5.0	
Ienca <i>et al</i> [58], 2020	Observational	1770	Elipse	4	4.9 ± 2.0	13.5 ± 5.8	14.2 ± 5.0	67.0 ± 64.1
Genco <i>et al</i> [59], 2018	Observational	38	Elipse	4	4.2	12.7	11.6	26
Taha <i>et al</i> [77], 2020	Observational	96	Elipse	4	4.9 ± 2.0	11.2 ± 5.1	12.1 ± 5.2	
Ponce <i>et al</i> [47], 2015	RCT	187/139	ReShapeDuo diet/exercise	6				25.1 ± 1.6/11.3 ± 1.9
Agnihotri <i>et al</i> [50], 2018	Observational	202	ReShapeDuo	6		11.7 ± 7.3	11.4 ± 6.7	29.9 ± 18.2

BMI: Body mass index; %TWL: Percentage total weight loss; %EWL: Percentage excess weight loss; RCT: Randomised controlled trial.

Classical Orbera

In 2016 Moura *et al*[62] analyzed 9 out of 12 collected randomised controlled trials (RCTs), all between 1990 and 2014, in an effort to assess the effectiveness of the Orbera IGB-plus-diet against sham balloon-plus-diet. This meta-analysis found the balloon/diet treatment to be more effective than the sham/diet; the former obese patients experienced a higher BMI loss, with a mean difference of 1.41 kg/m² (95%CI: -2.17 to -0.64, *P* = 0.0003) and a higher weight loss with a mean difference of 3.55 Kg (95%CI: -6.20 to -0.90, *P* = 0.009). Regarding %EWL, a higher %value was found by the

Student's *t* test in balloon groups, with a mean difference of 14.0% compared to the sham group; however, no significant difference was found between the groups by quantitative analysis, due to a significant heterogeneity of the studies. Furthermore, there are some serious limitations in the study: besides the long period of time covered by the collected RCTs, the main problem is that some of these studies were conducted in the early years of Orbera use; the second is the small number of patients (from 8 to 31 per study group) in all studies except one, which included 187 patients and 139 controls.

Since it is recommended that the Orbera IGB be filled with a volume, ranging between 400 and 700 mL of saline, Kumar *et al*[63] decided to correlate the balloon filling volume to clinically relevant endpoints, namely weight loss outcomes, balloon tolerability, and adverse events. This review, by the inclusion of 44 studies (5549 patients) demonstrating a low risk of publication bias, remains by far the largest meta-analysis of studies dealing with only Orbera balloons. Meta-analysis did not reveal any statistically significant association between filling volumes, between 400 and 700 mL, the percentage of TBWL being 13.2% (95% CI: 12.3–14.0) at 6 mo for all patients. The authors attributed the negative findings to the relationship between balloon size and volume: the diameter of a 400-mL saline-filled balloon is 9.14 cm, while those of a 700-mL is only 20% wider at 11.0 cm. Similarly, there was no association between balloon filling volume and early removal rates ($P = 0.1$), gastroesophageal reflux symptoms ($P = 0.64$), or gastric ulcer rates ($P = 0.09$). However, they recommend the balloon be inflated with a volume of 600–650 mL, since such a volume—inexplicably—reduces esophagitis: 9.4% *vs* 2.4% for a volume higher than 600 mL ($P < 0.001$), and migration rates: 2.26% *vs* 0.5% for a volume higher than 600 mL ($P = 0.004$).

Additionally, Yorke *et al*[64] reported, in their systematic review which included 26 studies (6101 patients), a reduction in body weight of 15.7 ± 5.3 kg and of BMI of 5.9 ± 1.0 kg/m², although 25 of the 26 are case series and not RCTs. Furthermore, they presented a percentage of 23.3% of patients experiencing nausea and vomiting, and 19.9% epigastric pain; the incidence of mortality was 0.05%, the 0.1% attributed to gastric perforation.

Although meta-analyses are certainly considered more reliable because they provide cumulative information from RCTs well-controlled for their reliability, there are many serious problems in the subject analyzed: (1) randomized studies of balloon treatment against sham treatment are very few and with a small number of cases; (2) not all studies included in a meta-analysis provide the same information regarding weight loss assessment parameters; and (3) studies comparing balloon types are also few, for two reasons: there are even now no observational studies with a large number of patients and no follow-up for most of the new balloons. The Orbera balloon, on the other hand, has a long history of clinical application and is thus considered trustworthy and reliable by the clinician, deterring many clinicians from changing from the well-known and safe Orbera just for the sake of a study. Thus, observational studies with a large number of patients were unavoidably used in the present analysis.

The most populated retrospective study (2515 patients) from the data-base of the Italian Collaborative Study Group, Genco *et al*[65] in 2005 reported a mean BMI reduction of 4.9 ± 12.7 (range, 0–25 kg/m²) at 6 mo; from 44.4 ± 7.8 (range, 28–79.1 kg/m²) to 35.4 ± 11.8 (range, 24–73 kg/m²), and a mean EWL from 59.5 ± 29.8 (range, 16–210 kg) to 33.9 ± 18.7 (range, 0–87 kg), accompanied by a sign of resolution of diabetes and arterial hypertension in the majority of cases. Intolerance leading to early removal of the Bioenterics IGB was evidenced in 11 out of 2515 (0.44%) patients, while the overall complication rate was relatively low (2.8%).

A case series for 500 consecutive patients treated with the Bioenterics IGB, who were recruited from a single center and followed-up for a 5 year period was reported by Kotzampassi *et al*[13]. There was a mean body weight loss of 21.19 ± 10.3 kg or a 16.79% reduction, a mean BMI reduction of 7.39 ± 3.57 kg/m² or 16.89%, and a percent EWL of 38.09 ± 20.18 , meaning that a target of more than 20% EWL had been achieved in 83% of patients at the time of balloon removal. At the 60 mo follow-up, a total of 195 patients completed the study and were found to have retained a weight loss of 7.26 ± 5.41 kg, a BMI reduction of 2.53 ± 1.85 kg/m², and a %EWL of 12.97 ± 8.54 . At this time, 46 out of the 195 (23%) retained %EWL greater than 20%. The authors comment that those obese patients who lost 80% of their total weight loss during the first 3 mo of the 6-mo treatment, succeeded in maintaining a percent EWL of > 20 long-term after BIB removal: more precisely, this cutoff point was achieved in 83% at the time of removal and in 53%, 27%, and 23% at 12-, 24-, and 60-mo follow-up[13]. Quite similar were the results of a meta-analysis of 7 studies (409 patients) reporting a mean weight loss of 12.9 ± 0.8 kg at 3 mo and 16 ± 0.9 at 6 mo, meaning that 80% of the weight loss was achieved within the first 3 mo of treatment[66].

Similarly, in a large series of 714 consecutive Spanish patients treated with the BioEnterics IGB (now Orbera), Lopez-Nava *et al*[67] found their initial mean weight to be 106.3 ± 21.5 kg (range, 68–190), mean BMI 37.6 ± 5.7 kg/m² (range, 31–57) and mean EW 56.3 ± 27.1 (range, 16–205 kg). After balloon removal at 6 mo, mean weight was 94.7 ± 22 (range, 52–160 kg); mean BMI 31.1 ± 7.2 (range, 24–48 kg/m²), mean %EWL 41.6 ± 21.8 (range, 0–77), mean weight loss 18.8 ± 9 (range, 0–45 kg); mean BMI loss 6.5 ± 12.7 (range, 0–21 kg/m²); and mean %EBL was 44.5 ± 22.6 (range, 0–81).

In 2015 American Society for Gastrointestinal Endoscopy (ASGE)[25] published a meta-analysis of 17 studies with 1638 patients which demonstrated a percentage of excess weight loss of 25.44% (95%CI: 21.47%–29.41%) with the Orbera balloon at 12 mo and a percentage of total weight loss of 11.27% (95%CI: 8.17%–14.36%) at 12 mo after implantation; thus they considered the Orbera balloon an appropriate treatment option since it exceeded the threshold of the preservation and incorporation of valuable endoscopic innovations of 5% TBWL.

In 2018, 39 Brazilian expert endoscopists[19] reached a consensus on guidelines on indications, patient selection, filling volume, techniques of insertion and removal and adverse events, based on their experience with 41.863 balloons–32.735 subjects with the non-adjustable fluid-filled Orbera (78.2%), another 16.9% with similar balloons, such as the Silimed, 1020 patients (2.4%) with the adjustable fluid-filled balloon Spatz and another 2.5% of cases with the Heliosphere air-filled balloon. The mean percentage total weight loss (%TWL) was $18.4\% \pm 2.9\%$, ranging from 13% to 25% and the mean BMI reduction was 7.2 ± 3.1 kg/m², ranging from 3.5 to 18.0. The total early removal rate due to intolerance was 2.2% (928 cases)–more common with the adjustable balloon (2.5% in 1020 subjects), and rather uncommon (0.8%) with the Heliosphere air-filled balloon. The adverse event rate after the adaptation period was reported at 2.5%, the most common being 0.9% hyperinflation and 0.8% spontaneous deflation of the device. Finally, there were only 3 deaths; a gastric rupture due to overfeeding in a super-obese patient, a pulmonary aspiration with vomiting, and a pulmonary embolism, which may not have been directly attributable to the balloon.

The most recently published study was that from 5 private clinics in Brazil (2000–2017) by Fittipaldi-Fernandez *et al*[68], which included 5874 patients in whom a liquid-filled balloon not named, but having characteristics intimating the Orbera was placed (600–700 mL saline). After 6 to 7 mo, patients were found to have a weight loss of 19.13 ± 8.86 kg, and a %TWL of $18.42 \pm 7.25\%$, treatment success rate, i.e. rate of patients achieving a %TWL over 10%, being 85%. The %EWL was $65.66 \pm 36.24\%$, while BMI also decreased significantly, from 36.94 ± 5.67 to 30.08 ± 5.06 kg/m², $P < 0.0001$.

Air-filled heliosphere

Over time, new balloons have been designed, keeping the initial idea of the Orbera–space-occupation in the stomach–but looking to improve the characteristics responsible for the adverse events of nausea and vomiting early after implantation, i.e. the combination of large volume and weight of the saline filled balloon. Thus, in 2017 Saber *et al*[69] were the first to introduce the air-filled balloon in their meta-analysis. They analyzed a total of 20 RCTs (13 with the fluid-filled Orbera balloon and 7 with air-filled balloons) involving 1195 patients assessed prior to, at 3 mo after balloon placement, and upon its removal. Unfortunately, from the 7 studies – 190 cases only – relating to air-filled balloons, 6 concluded that the air-filled balloons were not effective. The overall meta-analysis, regardless of the balloon type, revealed a significant reduction of 1.59 and 1.34 kg/m² for overall and for 3-mo BMI, respectively; a significant reduction of 14.25 and 11.16% for overall and > 3-mo percentage of excess weight loss, respectively; and a significant reduction of 2.81, 1.62, and 4.09 % for overall, 3-mo, and > 3-mo percent of weight loss, respectively. Overall a significant difference was calculated that favored the fluid-filled over air-filled IGBs; however, data was available only for a 3-mo study period comparison ($P = 0.02$). In general, due to the large heterogeneity within the studies (fluid and air-filled) the efficacy of all IGBs appears to be less impressive. However, generally speaking, the gas-filled balloons have better tolerance after implantation, but result in less weight loss in comparison to the fluid-filled[27].

Along the same line, Bazerbach *et al*[52] analyzed 15 RCTs involving patients treated with FDA approved, fluid-filled (Orbera; 12 studies, ReShape Duo; 1 study) or air-filled balloons (Heliosphere; 1 study, Obalon; 1 study) for at least 6-mo compared with another balloon, sham-balloon, or open-label control groups, in an effort to assess the effectiveness and tolerability of each. In meta-analysis, the fluid-filled devices were found superior in achieving a significant change of %TBWL, in 96.8% and 96.6% of cases at 6 and 12 mo, respectively: the Orbera resulted in a 6.72% reduction of total body weight (95%CI: 5.55, 7.89); and the ReShape Duo 4% (95%CI: 2.69, 5.31) as

opposed to the air-filled balloons Heliosphere and Obalon, which achieved 6.71% (95%CI: 0.82, 14.23) and 3.3% (95%CI: 2.30, 4.30), respectively. Although the fluid-filled balloons had the greater likelihood of being superior in achieving %TBWL, in the present meta-analysis the Orbera was finally associated with a non-significant difference in relation to the gas-filled Heliosphere 2.20% (-0.76, 5.16); the statistical findings probably relating both to the heterogeneity and small number of studies (Orbera $n = 12$ *vs* one for each other balloon type) for pair-wise comparisons. Finally, fluid-filled balloons were considered to be associated with a higher rate of intolerance; the combination of their high volume and weight have a profound impact on gastric motility, leading to a delay in gastric emptying of solids and thus to the increased sense of fullness and satiation, and as a result to body weight loss.

Adjustable Spatz

Another requirement in the Tarpon Springs Consensus meeting was that the balloon volume capacity be variable and adjustable, according to patient tolerance and success in losing weight. This was achieved with the Spatz adjustable balloon system by a rather complex and sophisticated mechanism which allows the filling volume to be adjusted, up or down, after implantation. Modifications ultimately resulted in the 3rd generation of adjustable balloons, the Spatz3.

One of the first available comparative studies carried out between 2010 and 2014, was that of Russo *et al*[70]. It comprised a small patient group: 20 elderly patients in whom the BioEnterics IGB was implanted and 10 patients given the Spatz Adjustable Balloon System. The two groups were compared in terms of weight loss, complications, and maintenance of weight after removal. They had a BMI ranging between 37 to 46 kg/m² and a weight range of 103 to 165 kg. For both procedures, median BMI at the end of treatment was 32 ± 2 kg/m² and the median weight loss was 20 ± 3 kg. At 6 mo follow-up, weight gains were 6 ± 1.5 kg for the 10 patients with the Bioenterics balloon *vs* 6 ± 2 kg for the five patients with the Spatz. In 2 out of each group the balloon was removed early, due to intolerance. In one additional BioEnterics balloon patient the balloon was removed due to deflation; and in 3 additional Spatz patients the balloon was adjusted due to intolerance, but finally two of the latter achieved no significant weight loss.

Abu Dayyeh *et al*[71], at 8 US centers, studied the efficacy and safety of the Spatz3 in 187 patients in relation to lifestyle modification alone for a 32-wk period. Percentage total weight loss was $14.9 \pm 7.2\%$ in the treatment group compared to $3.6 \pm 5.8\%$ in the control group; an additional 4.7% TBWL was achieved after upward volume adjustment between weeks 18 and 32 and more than 40% of the treatment group had maintained their weight loss at 56wks. Serious adverse events were reported at a rate of 5.3%, 4% of which were attributed to gastric ulcers.

Fittipaldi-Fernandez *et al*[45] presented 180 patients randomly divided into a Spatz3 balloon group in which the balloon was inflated with 600 mL of saline, the volume remaining stable throughout treatment, and a second Spatz3 balloon group in which the balloon volume was adjusted upward with 250 mL more saline. At removal, after 7.12 ± 1.63 mo, BMI was found decreased from 39.51 to 32.84 kg/m² ($P < 0.0001$), body weight from 111.87 to 90.28 kg ($P < 0.0001$), and excess weight from 41.55 to 22.99 kg ($P < 0.0001$). The volume adjustment resulted in greater mean weight loss of only 4.35 kg, but no increased %TWL, %EWL, or decrease in BMI compared with the not-adjusted group. The authors conclude that the Spatz3 balloon seems to be an effective weight loss procedure, although it was found to be related to a higher morbidity (16.14%) in relation to traditional balloons.

Schwaab *et al*[72] 2020 published a cross-sectional study of 470 overweight or obese patients who were treated by either a non-adjustable IGB (Orbera), 326 subjects implanted for 6 mo; or an adjustable balloon (Spatz) in 144 subjects for up to 12 mo. A total of 414 out of 470 individuals completed the treatment period. The Orbera-treated patients achieved a %TBWL of $15.4 \pm 7\%$ and the Spatz-treated patients $15.5 \pm 9.6\%$. Similarly, 264 Orbera-treated patients (88.6%) against 93 Spatz-treated patients (80.2%) achieved a %EWL over 25%, $P = 0.038$. However, the balloon volume adjustment seems not to have made a significant difference: within the Spatz group, 67 (85.9%) patients subjected to re-adjustment of balloon volume *vs* 27 (73%) not subjected to re-adjustment achieved a %EWL over 25%, $P = 0.203$.

Swallowable Obalon and Elipse

The Obalon, the gas-filled, swallowable IGB, designed to allow easy gastric volume titration by using additional balloons was studied against a lifestyle modification-alone group by Sullivan *et al*[73] (the SMART trial). A total of 387 patients were included from 15 centers in United States; 185 patients swallowed at least one Obalon

capsule and 181 a sham capsule. After a 6 mo treatment period, the Obalon resulted in a %TBWL of $6.6 \pm 5.1\%$ in relation to $3.4 \pm 5.0\%$ in the control group, $P = 0.0354$, the difference being 3.2% (95%CI: 2.2, 4.2); the responder rate was 62.1% in the Obalon group, the end-point being 35% and 30.7% in control group, $P < 0.0001$. At 48 wk, subjects who had achieved a weight loss at week 24, maintained their loss at a rate of 88.5% ($7.8 \pm 4.4\%$ TBWL at 24 wk and $6.9 \pm 6.5\%$ TBWL at 48 wk, $n = 151$). Finally, they presented 0.3% severe adverse events, including one bleeding gastric ulcer.

There are few previously published clinical studies, with only a small number of participants: Mion *et al*[54] in 2013 first reported a pilot study in 17 patients – 43 balloons – to assess the efficacy of the Obalon for weight loss over a 3mo study period. There was a median %EWL of 36.2 (range 0 to 118%) and a BMI reduction from 31.0 kg/m^2 to 28.1 kg/m^2 , with no serious side-effects. Similarly, in 17 cases of pediatric/adolescent morbid obesity De Peppo *et al*[56] in 2017 reported a statistically significant decrease ($P > 0.05$) of mean BMI value from $35.27 \pm 5.89 \text{ kg/m}^2$ to $32.25 \pm 7.1 \text{ kg/m}^2$; and a %EWL of 20.1 ± 9.8 (range 2.3 to 35.1) after 3 mo of treatment.

The Elipse IGB is a swallowable fluid-filled balloon, which is spontaneously deflated at week 16 and passes through the gut to be self-removed through the natural orifice; it can thus be considered the ‘evolution’ of the Obalon, since it is both placed and removed without the need of anesthesia and endoscopy. Recently, Ienca *et al*[58] published the largest trial comprising 1770 consecutive Elipse patients. After 4 mo treatment a weight loss of $13.5 \pm 5.8 \text{ kg}$, a %EWL of 67.0 ± 64.1 , a BMI reduction of 4.9 ± 2.0 , and a %TBWL 14.2 ± 5.0 was reported. Eleven emptied balloons (0.6%) were vomited and another 52 (2.9%) were endoscopically removed due to patient intolerance. Three deflated balloons led to small bowel obstruction, requiring surgical intervention.

The difference in the reliability of the statistical results depends on the number of patients in the study sample, as well as the use of a multidisciplinary approach and counseling for these patients; thus Genco *et al*[59] presenting their early experience with the Elipse balloon in only 38 Italian patients who received a multidisciplinary approach, reported a mean weight loss of 12.7 kg, a %EWL of 26%, a mean BMI reduction of 4.2 kg/m^2 , and a %TBWL of 11.6%.

At the same time, Vantanasiri *et al*[74] 2020 published a systematic review and meta-analysis of six prospective studies of the Elipse balloon, involving 2013 patients. The largest study was that already discussed (Ienca *et al*[58]–1770 patients) and the other 5 were small cohort studies (30 to 135 patients) with high heterogeneity. The mean %TWL after completion of treatment (4 to 6 mo) was 12.8% (95%CI: 11.6%–13.9%; $I^2 = 83\%$) and at 12 mo 10.9% (95%CI: 5.0%–16.9%, $I^2 = 98\%$). However, the long-term effects after the Elipse balloon treatment still remain unclear. Additionally, there is no study comparing the Elipse balloon with any other IGB. A rate of 0.2% of serious adverse events was reported; three patients suffered small bowel obstruction due to a deflated balloon and one experienced gastric perforation, resolved surgically. Although it seems to be safe and easily handled, its application by an inexperienced bariatric endoscopist, as no endoscopy is needed, poses the risk of overlooking or misunderstanding a serious adverse event, as Angrisani *et al*[75] points out in his commentary entitled “the pitfalls of excessive simplicity”.

In the same year another meta-analysis of 7 Elipse balloon-studies, involving 2152 patients was conducted by Ramai *et al*[76], with the same disadvantage as the previous one: only Ienca’s study[58] had 1770 cases, while all other six studies ranged from 12 to 135 cases, with high heterogeneity. The results, however, were quite similar: %TBWL was 12.2% (95%CI: 10.1–14.3, $I^2 = 94\%$) and %EBWL was 49.1% (95%CI: 30.6–67.5, $I^2 = 97\%$). Pooled adverse events were 37.5% abdominal pain, 29.6% vomiting, 15.4% diarrhea and 0.5% small bowel obstruction.

Finally, a recent study of 96 patients from Egypt, not included in the previous meta-analyses, was published by Taha *et al*[77], 2020. After the 4 mo period following implantation the %TBWL was $12.1 \pm 5.2\%$, the mean weight loss was $11.2 \pm 5.1 \text{ kg}$, and the mean BMI reduction was $4.9 \pm 2.0 \text{ kg/m}^2$. The authors also reported 3.1% intolerance, resulting in early balloon removal; one (1.1%) balloon deflated early and was uneventfully passed, and, surprisingly, there were 11.5% attacks of diarrhea and 21.9% of colicky abdominal pain for a week around the time of balloon self-deflation.

Double balloon

Regarding the ReShape Duo IGB, Ponce *et al*[48], 2013 published the first results after its placement in 21 subjects *vs* 9 controls-diet only. These data belong to the phase 1 portion of the REDUCE study, which stopped prematurely to be redesigned, since its primary endpoints seemed to be unachieved. At 6mo these patients presented no significant difference in %EWL, although their findings were not negligible ($31.8\% \pm$

21.3% in the balloon group and $18.3\% \pm 20.9\%$ in the controls, respectively, $P = 0.1371$); a percentage of 64% of balloon-treated maintained their weight loss 6mo after balloon removal.

Two years thereafter Ponce *et al*[47] presented the final results of the REDUCE pivotal trial: the ReShape balloon-treated patients ($n = 187$) had a $25.1 \pm 1.6\%$ (mean \pm SE) %EWL, 48.8% of cases achieving a %EWL over 25% *vs* $11.3 \pm 1.9\%$ in the diet and exercise only control patients ($n = 139$), $P = 0.0041$; sudden balloon deflation occurred in 6% of cases, but no migrations; balloon intolerance led to early balloon removal in 9%. Gastric ulcers at the level of gastric incisura were initially observed in 35% of patients due to pressure of the distal tip of the device. After a minor modification to make it shorter, smoother and with a 50% reduced diameter, the frequency of ulcers dropped to 10%.

Another study with 202 patients in whom the Reshape Duo balloon had been placed was published in 2018 by Agnihotri *et al*[50]. At 6 mo they reported a statistically significant decrease ($P < 0.001$) in BMI values from $36.8 \pm 8.4 \text{ kg/m}^2$ in baseline to $32.8 \pm 6.7 \text{ kg/m}^2$, a %TBWL of $11.4 \pm 6.7\%$ and a %EWL of $29.9 \pm 18.2\%$. The authors also referred to a high rate of nausea, vomiting and abdominal pain in the early days: 66.4%, 49% and 25.2%, respectively, leading to a 6.4% of early balloon removal. Finally, there was only one case of balloon migration, resulting in a small bowel obstruction and requiring surgical intervention.

Finally, Suchartlikitwong *et al*[49] in 2019 presented their experience in 35 cases using the Reshape Duo balloon. They reported a 7% decrease in BMI value, or $2.7 \pm 2.9 \text{ kg/m}^2$, $P < 0.001$. Nausea and vomiting presented in 23% of patients, requiring balloon removal in two. 3% of patients suffered gastric erosions, but one patient with a history of ulcer experienced gastric hemorrhage requiring blood transfusion. Finally, one patient required surgery for balloon removal after deflation and distal movement leading to bowel obstruction.

Efficacy and tolerability

Looking for comparative assessment of the efficacy of IGBs, Kotinda *et al*[12] performed a systematic review and meta-analysis of 13 randomized controlled trials (1523 overweight and obese adults) focusing on the efficacy of IGBs for weight loss. Eight studies used the Orbera, one the Orbera or Heliosphere (gas-filled), two the ReShape Duo, and one each the Spatz and the Obalon (gas-filled). They found a highly significant difference in mean %EWL of 17.98% (95%CI: 8.37-27.58, $P < 0.00001$) in the balloon group in comparison to the sham/life-style modification group. In the subgroup analysis there was no significant difference between balloon types for this outcome. When assessing data in respect to %TWL, they also found a highly significant difference in mean %TWL of 4.40% (95%CI: 1.37-7.43, $P < 0.00001$), but, in subgroup analysis, this effect was mostly related to the Spatz balloon [11.30 (9.77, 12.83)], although other balloons (Obalon, Orbera, and ReShape Duo) also had favorable outcomes. However, on analysis of the data in relation to BMI loss, a significant difference of 2.13 Kg/m^2 (95%CI: 0.57-3.68, $P < 0.00001$) was found in the balloon group, while in subgroup analysis it was mainly due to the Orbera balloon [2.49 (0.19, 4.80)], although the Obalon, Heliosphere, and ReShape Duo also showed favorable results. They finally analyzed the values of absolute weight loss, not commonly found as a study parameter. From a total of 7 studies (1005 participants), a mean difference of 6.12 kg (95%CI: 3.80 to 8.44, $P < 0.00001$), in favor of the balloon group was evident, mainly achieved by the Orbera balloon [7.88 (3.81-11.95)], although the Obalon and the ReShape Duo also had positive outcomes.

IGBs are space-occupying devices designed to induce satiety and thus reduce food intake, which ultimately results in weight loss; it is reasonable and obvious to expect that the sudden but permanent onset of fullness of the stomach by means of increasing the balloon volume, and, in the case of fluid-filled balloons, of the additional sensation of weight could be 'translated' by the obese as a sense of persistent nausea and/or tendency to vomit, as well as generalized abdominal pain and/or discomfort, back pain, and acid reflux. These accommodative symptoms are common after balloon placement, but are usually self-limiting. In terms of patient tolerance of the IGB, and especially during the first 1-2 wk of placement, Trang *et al*[78] in 2018 conducted a systematic review and meta-analysis of the incidence of nausea and vomiting after IGB placement in bariatric patients. In this review of 10 studies they focused on four types of balloons: the fluid-filled Orbera, the ReShape Duo, the Elipse, and the gas-filled Obalon, and calculated the meta-analytic rates of nausea and vomiting based on adverse event sample size. A total of 564 out of 938 patients reported nausea; 63.33% (95%CI: 61.49%-65.16%), and 507 patients reported vomiting; 55.29% (95%CI: 53.59%-56.99%). Fluid-filled balloons were placed in obese participants in 7 studies:

394 and 434 out of 575 patients experienced nausea and vomiting respectively; rates of 72.99% (95%CI: 69.54%–76.45%) and 76.95% (95%CI: 73.86%–80.05%), respectively. The gas-filled Obalon balloon, was used in 3 studies: 200 and 62 out of 363 patients reported nausea and vomiting, respectively; rates of 55.10% (95%CI: 50.00%–60.00%) and 16.20% (95%CI: 12.43%–19.96%), respectively. Further analysis of fluid-filled balloons, *i.e.* the Orbera, ReShape Duo, and Elipse, revealed that the Orbera balloon caused the highest rates of nausea and vomiting compared to all other balloons. Three studies using the Orbera reported nausea and vomiting in 195 and 177 out of 248 individuals respectively; rates of 81.97% (95%CI: 77.00%–87.00%) and 72.16% (95%CI: 66.65%–77.67%) respectively. Comparatively, 2 studies with the ReShape and another 2 with the Elipse balloons reported nausea and vomiting respectively in 178 and 246 out of 285 patients and in 21 and 23 out of 42 patients; rates of 63.18% (95%CI: 58.00%–69.00%) and 86.42% (95%CI: 82.44%–90.39%) for the ReShape and 51.42% (95%CI: 46.00%–57.00%) and 12.48% (95%CI: 8.51%–16.44%), for the Elipse, respectively. The authors comment that the large variation rate of symptoms, even that of vomiting, [a relatively objective parameter], apart from the type of balloon used, might be related to the type, the dosage and the frequency of medications prescribed during any specific study.

Gastric emptying and weight loss

Based on the general hypothesis that the rates of gastric emptying and the stomach accommodation volume regulate food intake, appetite, satiation and satiety, and are thus associated with postprandial fullness, bloating, and finally weight loss, Vargas *et al*[24] analyzed the changes in time of gastric emptying in 19 studies, after either IGB placement or bariatric surgery. Fluid-filled balloons (3 studies) increased gastric emptying time by 116 min (95%CI: 29.4–203.4 min) as opposed to air-filled balloons (2 studies) which did not result in a statistically significant difference in gastric emptying time [–2.9 min (95%CI: –21.7 to 15.9 min)]. When authors analyzed pooled data of 5 studies, the mean change in gastric emptying time was only 42.7 min, (non-significant); however, meta-regression revealed prolongation of gastric emptying time which was associated with a higher percentage of total body weight lost at 6 mo ($P = 0.05$). When the association between gastric emptying time and weight loss was analyzed in fluid-filled (Orbera) balloons, the significantly prolonged gastric emptying time led to a greater excess weight loss at 6 mo ($P = 0.04$), potentially explaining the difference in efficacy and tolerance found across air *vs* fluid-filled balloons[52].

Quality of life and mental health

Gadd *et al*[79] tried to analyze the impact of endoscopic bariatric procedures, IGBs included, in the improvement of quality of life (QoL) and mental health, assessed by using a validated tool. Twenty studies published between 2008 and 2019 with a total number of 876 participants (77% female) were included, evaluating five different endoscopic procedures. Fourteen out of 20 referred to IGBs and finally 9 (371 participants - 350 at 6 to 76-mo follow-up) were included *via* meta-analysis. IGB placement was associated with a significant improvement in QoL (SMD: 0.78; 95%CI: 0.56, 1.00; $P = 0.05$; I²: 48%). Following sensitivity analysis, IGB placement was associated with a large improvement in post-procedural QoL (SMD: 0.85; 95%CI: 0.69, 1.02; $P < 0.00001$; I²: 7%). Five studies (367 participants at 6 to 76 mo follow-up) out of the nine were analyzed in respect to mental health, depression, and anxiety, and IGBs revealed a significant improvement (SMD: 0.86; 95%CI: 0.29, 1.42; $P = 0.003$; I² = 92%). All studies correlate improvement of quality of life, mental health, depression, and anxiety with significant improvement in obesity related parameters. The two studies (Guedes *et al*[80] and Deliopoulou *et al*[81]) with the largest improvements in mental health also had the greatest weight loss. However, the authors commented that all these patients received multidisciplinary support in the form of unlimited 24-h phone support, follow-up by a dietitian and nutrition counseling, cognitive behavioral therapy, and/or a lifestyle modification programme. The greater the support, the more significant the improvement in mental health and weight loss.

DISCUSSION

The IGB is a well-established therapeutic tool for the treatment of obesity, being the most popular technique of those included under the concept of endoscopic bariatric and metabolic therapies, which have emerged over the years, to provide alternative options beyond lifestyle modifications, pharmacotherapy, and surgery. It is actually a

completely non-invasive endoscopic technique, in the absolute sense of the term, since its leading advantage is that it does not interfere permanently with the anatomy and volume-shaping of the stomach by means of interventions in the gastric wall, such as sutures, stomas, thermal destruction of the mucosa, *etc.*, used by other modern endoscopic techniques.

Thus, IGB insertion represents a generally safe, easy to perform, adjustable, reversible, and reproducible endoscopic gastric restriction procedure, successfully applied for weight loss over the last 30 years. It covers a broad spectrum of indications from the overweight to the obese individual who does not fulfill the criteria for bariatric surgery, up to the morbidly obese, who qualifies for bariatric surgery but has uncontrolled co-morbidities causing her/him to be of high-risk for anesthesia and surgery or denied anesthesia and/or surgery, or its use as a bridge to bariatric surgery, and, finally, to anyone who just needs to achieve limited weight reduction, either prior to surgery of whatever kind and for whatever reason or merely for aesthetic purposes [51,82,83]. Generally speaking, the specific indications for balloon implantation for each candidate for such treatment must be built on the absolute judgment of the treating physician or the multidisciplinary working team; however, the positive response, that is the weight loss, is due exclusively to the responsibility of the patient to strictly adhere to a diet/exercise program and follow-up sessions throughout the treatment period, whatever type of balloon has been used.

To reconfirm the advantages of the procedure, we use the concepts formulated by Fobi and Baltasar to define quality indicators for bariatric surgery procedures which should also be somehow applicable to bariatric endoscopy [84]. According to these criteria any relevant procedure should be: (1) safe, exhibiting a mortality of less than 1%, and a morbidity of less than 10%; (2) effective and long-lasting, with excess weight loss of over 50% in more than 75% of patients at 5 year follow-up; (3) reproducible, so the results of different centers performing the procedure provide a similar, easy learning curve; (4) provide good quality of life; (5) require revisions less than 2%; (6) have minimal adverse effects; and (7) be easily reversible, from an anatomical or functional perspective.

However, IGB effectiveness, as a non-permanent intervention, remains debatable, as there is no consensus on the proportion of weight loss that should be achieved for an endoscopic procedure to be considered effective and thus be recommended for clinical use. The ASGE [25] defined a mean minimum threshold of 25% EWL, measured at 12 mo, for any endoscopic bariatric and metabolic therapy intended as a primary obesity intervention, and 5% of %TBWL as the absolute minimum threshold for any non-primary intervention, such as bridging therapy. It also recommended that the risk of serious adverse events related to the procedure be equal or less than 5%-most of the reported adverse events with IGBs (nausea, vomiting, abdominal pain) are classified as mild to moderate, according to ASGE Quality Task Force recommendations [25].

Today there are already six commercially available balloons, three of which are FDA-approved; some of them having one or more 'clones', available in different parts of the world. Chronologically, the first balloon designed and manufactured according to the Tarpon Springs Directives was the Bioenterics IGB (now available as the Orbera) [20]. Based on the advantages and disadvantages of this balloon, there have been many attempts to develop new balloons, incorporating technical improvements, but without compromising the baseline characteristics of the Orbera, which has long remained at the top of the field.

The main disadvantages of the Orbera balloon, which should be improved, are the following: (1) The balloon placement and removal must be performed by means of endoscopy, and at least the removal to be done under conscious sedation, which increases not only the overall cost of treatment, but also the potential risks of both endoscopy and anesthesia; (2) The first week after balloon placement patients experience some degree of discomfort, in the form of nausea, vomiting and epigastric pain, well-attributed to the 600-700 gr of saline with which the balloon is inflated. This etiology is true for all fluid-filled balloons. On the other hand, this is the feature which makes the fluid-filled devices more effective in weight loss, in comparison to gas-filled balloons; (3) The effectiveness of the Orbera and of other fluid-filled balloons is generally satisfactory, especially when combined with diet and exercise counseling and the patient is under a multidisciplinary assessment group, not excluding, occasionally, psychiatric supervision. After balloon removal, however, the maintenance of good results in weight loss varies in the long-term, depending on many subject-related and not balloon-related factors, as, exactly similarly, occurs in real life; ex-obese individuals must maintain the new habits and lifestyle, feeding re-education and physical exercise, but mainly the behavioral modification and positive psychological state resulting from the changes in their physical appearance (body shape),

physical functioning through improvements in co-morbidities, and social functioning due to increased self-esteem[13,85,86].

Based on this, some argue that a long-lasting balloon such as one with 12 mo lifespan in the stomach (the Orbera365 and the Spatz3) may be more useful since it allows more time for life-style re-education to become habituated[87,88]. On the other hand, it is well known that the greatest weight loss, even up to 80% of the total %EWL, is achieved within the first 3 mo of balloon-life in the stomach; weight loss then continues, but at a reduced percent monthly[13,66,89]. Thus, a 12-mo lifespan balloon probably offers questionable benefits. It might also be suggested that long-term contact with gastric mucosa, especially if the balloon is not totally smooth and spherical (Spatz3), could be more traumatic, possibly resulting in gastric mucosal erosions and bleeding.

The counter-argument would be that the 4 mo life-span of the Elipse could be considered an inadequate time to achieve the desired results. Although the 6 mo balloons achieve the greatest weight loss within the first 3 mo, the additional 3 mo in the stomach is a time during which it works at very least as a space-occupying device preventing excessive food intake and consequently of early weight gain.

Unfortunately, there are no studies at all comparing the weight loss with the classical Orbera against the new Orbera365 - that is 6 mo *vs* 12 mo of the balloon remaining in the stomach. Theoretically, this could be an argument for inserting two consecutive balloons, but there is little evidence of success achieved by the second, which is why some authors recommend a time lapse between the first and second balloon[90,91]. In contrast, the application of the Spatz3 for 12 mo cannot be compared with the Orbera365, since the latter is designed as 'adjustable', meaning that at 3 mo, when the patient stops losing weight quickly, a volume of 250 mL of saline is added, changing both the volume and weight of the balloon, and thus the results. However, when compared, the weight loss between groups in which the Spatz3 balloons was adjusted or not, no significant difference was found[45].

Comparing the filling volume of the various liquid-filled balloons, it is clear that the volume of the balloon does not seem to directly determine weight loss. This was demonstrated in a study in which the Orbera balloon was filled with volumes of 400 mL to 700 mL[63], but also from the results of all studies with various balloons, with more or less the same volumes of saline. Furthermore, it is well known that short-term satiety is primarily affected by gastric distension and gastric volume; as we know from research that mechanical gastric balloon distension to a volume greater than 400 mL during meals significantly reduces oral intake[92,93]. However, it should be emphasized that gastric distension and gastric volume are related to the weight and volume of the 'food', rather than its energy content, thus decisions regarding food ingredients has to rely on the patient's choice to comply with dietary rules[23,92].

For this reason all patients must undergo a psychological screening before entering the process of balloon implantation[61,86]. This does not in any way mean that obese patients with bipolar disorders or other psychiatric diseases under medication should be excluded from treatment. On the contrary, it seems that there is a clear improvement in depression status with weight loss and the improvement of their body image[13,85,94], called by Spirou *et al*[95] the "psychological honeymoon period". In our opinion, a key component in their preliminary interview must be for the obese individuals to describe the social and psychological impact of obesity on their life, make a brief statement on their motivation to lose weight (for instance, to alleviate physical symptoms or to become more attractive/marriageable), and to recognize how they are affected by external factors, such as social support and reinforcement. This information - particularly the reason for strongly desiring to lose weight - should then be used at every follow-up session to inspire them to continue the effort towards weight loss or loss maintenance[13].

Another essential tool for achieving a significant and sustainable weight loss is the requirement for the patient to attend follow-up consultation sessions, which also bolster self-confidence. In a study analyzing 583 obese individuals treated with the Orbera balloon in respect to weight loss, the group of successful responders (%EWL more than 50%) and the group of poor responders (%EWL less than 20%) were compared. 85.2% of successful responders, $n = 162$, had attended the maximum of six interviews, whereas the 83.8% of the 105 poor responders attended fewer than four interviews[13,85,96]. Similar results were reported by Schwaab *et al*[72]: patients with more than four consultations achieved notably higher %EWL values (more than 18%, $P < 0.001$).

As has already been mentioned in the 'drawbacks' to the Orbera, the liquid-filled balloons have a higher rate of intolerance during the first week after implantation; which is why air-filled (Heliosphere bag) or gas-filled balloons (Obalon) were

designed. The Heliosphere has a volume of 550 mL, but a weight of only 30 gr, thus allowing a soft transition to new nutritional status, without nausea and vomiting, but in exchange for less weight loss in some studies. Some difficulty in balloon placement through gastric cardia has also been reported[12]. To overcome the same problem of early intolerance, the Spatz3 was designed with the unique feature of post-implantation volume control, meaning its volume can be reduced in case of early intolerance and, when symptoms cease, the volume can be increased. These procedures do, however, presuppose anesthesia and endoscopy[44,45].

The improvements and advances made in the design of the other balloons (the ReShape Duo, the Obalon and the Elipse) modifying the classic Orbera configuration, could be summarized as follows: The ReShape Dual balloon system[30,47] has been re-designed as two smaller, independent silicone spheres of 450 mL each, joined by a central, short, non-communicating flexible silicone shaft. This flexible balloon configuration allows them to conform to the natural anatomy of the stomach, while decreasing the chance of balloon intestinal migration should one of the balloons accidentally deflate[5,47,56,57]. Unfortunately, Apollo Endosurgery discontinued this product line after purchasing ReShape Medical Inc, CA, in 2018.

The Obalon and the Elipse balloons have the advantage of not requiring endoscopy for insertion and, in the case of the Elipse, for removal too, both being easily swallowable. Nevertheless, fluoroscopy is mandatory for proper positioning, because although the total cost of treatment is significantly reduced, as is the theoretical danger of complications due to anaesthesia and endoscopy, there is still a risk[59]. However, the endoscopy-free insertion carries its own disadvantages: the balloon is placed in a stomach with unknown mucosal pathology, and unknown anatomy, thus all the 'exclusions' described for the other balloons remain obscure (huge hiatus hernia, gastric ulcer/erosions, prior gastric surgery). The Elipse has the additional advantage of being degradable after a 4mo period, when it freely passes through the rectum.

Major complications related to IGB placement include esophageal/ gastric ulcerations and tears due to permanent mucosal irritation by the balloon or iatrogenic trauma and/or perforation during balloon insertion and, mainly, removal; and bowel obstruction, due to balloon self-deflation and migration to the gut[97]. According to the Tarpon Springs directives[20] for "the safe and effective balloon" a balloon must have "a smooth surface having low potential for causing erosions, ulcers or obstructions". The greatest conformity to this description is the Orbera. The early design flaw of the ReShape Duo, with the distal tip, was the cause of gastric ulceration in up to 35% of cases, which, however, dropped immediately to 10% after design modification[48]. Similarly, the Spatz3 balloon, although exactly meeting the criterion of being adjustable, has failed to fulfill the criterion of having a completely smooth surface, since it has a sort of 'tail' at the site of insertion of the filling valve[43]. This balloon has also been implicated in causing acute pancreatitis[98].

In a recent publication Stavrou *et al*[99] systematically reviewed PubMed and Scopus archived publications up to the end of 2018, describing Orbera-related life-threatening visceral complications, *i.e.* perforations and obstructions, and classified them according to blame: the device, the patient or the doctor. In a total of over 277000 balloons implanted worldwide by the end of September 2018, according to Apollo Endosurgery reports[100], 22 cases of gastric perforation, 2 cases of esophageal perforation and 10 cases of bowel obstruction were found. For the gastric perforation the endoscopist was responsible in 9 cases, the patient in 4, and the balloon itself in 9. For the 2 cases of esophageal perforation, the endoscopists were responsible, while for the 12 cases of bowel obstruction, the patient was responsible for 7 and the device for the other 5 cases.

CONCLUSION

As a final comment at the end of this analysis, we must underline that balloon placement, and even more balloon endoscopic removal should not be considered to be, in any way, a simple endoscopic procedure to be carried out by an inexperienced endoscopist. Individual doctors or even institutions without experience, accreditation, or the ability to resolve obesity-related or bariatric surgery-related complications must not undertake such procedures, if we do not want an increase in complications[95,101, 102]. This danger increases with the increased availability of swallowable balloons on the market. Their advertising and the ease of use, as presented, can become a disastrous trap if an uncertified and inexperienced doctor dares to use them. The fact that endoscopy is not mandatory and becomes a matter of patient choice removes the

necessity for a doctor with the appropriate training to be able to recognize and deal with any complication which might suddenly occur. This point is further emphasized in the latest published directives of the ASGE: "...training and skill acquisition with endoscopic bariatric techniques and technologies is mandatory before clinical application is undertaken, and should include didactic as well as hands-on practical education". And, furthermore, "...importantly, any practitioner who is interested in performing an endoscopic bariatric procedure should also be educated in the clinical management of obese patients," which means, have the ability to resolve complications[25].

From the above analyses, it is clear that: (1) There are no "good" and "bad" balloons, at first glance; all new balloons must be given an equal chance to be tested by experienced endoscopists before being judged; and (2) There is no special indication for the use of a particular balloon - all fit all stomachs. However, the use of one rather than another of the six balloons mentioned in this review, or between some others of lower cost, or of national manufacturers, relies on the absolute discretion of the physician, and not of the obese patient, and I personally never discuss it.

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Endoscopic retrograde cholangiopancreatography: Current practice and future research

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Author contributions: Sanders DJ and Kozarek RA contributed manuscript concept and inception; Sanders DJ, Bomman S and Krishnamoorthi R contributed drafting of manuscript; Sanders DJ, Bomman S and Krishnamoorthi R, Kozarek RA contributed critical review, revisions and final approval.

Conflict-of-interest statement: Dr. Sanders DJ and Dr. Bomman S has no conflicts of interest related to the nature or content of this article. Dr. Krishnamoorthi R receives research support from Boston Scientific. Dr. Kozarek RA receives research support from Boston Scientific Corporation and the National Institute of Health.

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a primarily diagnostic to therapeutic procedure in hepatobiliary and pancreatic disease. Most commonly, ERCPs are performed for choledocholithiasis with or without cholangitis, but improvements in technology and technique have allowed for management of pancreatic duct stones, benign and malignant strictures, and bile and pancreatic leaks. As an example of necessity driving innovation, the new disposable duodenoscopes have been introduced into practice. With the advantage of eliminating transmissible infections, they represent a paradigm shift in quality improvement within ERCP. With procedures becoming more complicated, the necessity for anesthesia involvement and safety of propofol use and general anesthesia has become better defined. The improvements in endoscopic ultrasound (EUS) have allowed for direct bile duct access and EUS facilitated bile duct access for ERCP. In patients with surgically altered anatomy, selective cannulation can be performed with overtube-assisted enteroscopy, laparoscopic surgery assistance, or the EUS-directed transgastric ERCP. Cholangioscopy and pancreatoscopy use has become ubiquitous with defined indications for large bile duct stones, indeterminate strictures, and hepatobiliary and pancreatic neoplasia. This review summarizes the recent advances in infection prevention, quality improvement, pancreaticobiliary access, and management of hepatobiliary and pancreatic diseases. Where appropriate, future research directions are included in each section.

Key Words: Cholangiopancreatography; Endoscopic retrograde; Cholangioscopy; Cannulation; Endoscopic ultrasound; Disposable duodenoscopes

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): A, A

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: March 19, 2021

Peer-review started: March 19, 2021

First decision: May 4, 2021

Revised: May 18, 2021

Accepted: July 9, 2021

Article in press: July 9, 2021

Published online: August 18, 2021

P-Reviewer: Chow WK, Espinel J, Matsubara S, Sato H

S-Editor: Gao CC

L-Editor: A

P-Editor: Li JH



Core Tip: Disposable duodenoscopes present a way to eliminate transmission of drug resistant infections. Access to single operator cholangioscopy and pancreatoscopy has made complex intraductal assessment and therapy more ubiquitous. Future research will clarify the role of endoscopic ultrasound bile duct access for variant anatomy or failed endoscopic retrograde cholangiopancreatography (ERCP), photodynamic therapy, and indomethacin and pancreas duct (PD) stents in post ERCP pancreatitis prophylaxis.

Citation: Sanders DJ, Bomman S, Krishnamoorthi R, Kozarek RA. Endoscopic retrograde cholangiopancreatography: Current practice and future research. *World J Gastrointest Endosc* 2021; 13(8): 260-274

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/260.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.260>

INTRODUCTION

This coronavirus disease 2019 (COVID-19) pandemic has changed our collective understanding of infection transmission, vaccine development, and the challenges of providing continuity of care in a rapidly evolving health care crisis. The evolution in endoscopic retrograde cholangiopancreatography (ERCP) has been more gradual, but certainly there have been periods of innovation punctuated by rapid change. Given the global pandemic, an area of interest with accelerated focus is the use of disposable duodenoscopes to break the chain of infection in ERCP. With rising concerns over reusable duodenoscopes implicated in nosocomial outbreaks, the trend toward transitioning to disposable components and completely disposable duodenoscopes has begun.

As highlighted in previous reviews, ERCP has moved from a diagnostic to primarily therapeutic procedure[1]. The therapeutic indications for ERCP include stones in the biliary and pancreatic ducts, benign and malignant strictures, and bile and pancreatic leaks[1]. Despite the near ubiquitous access to advanced radiology and endoscopic ultrasound (EUS) in North America, ERCP still has diagnostic indications in patients with a solitary dilated duct, cholangiocarcinoma, primary sclerosing cholangitis, and autoimmune cholangitis. This article will focus on the current state of practice for diagnosing and managing hepatobiliary and pancreatic disease with ERCP in 2021.

As competency-based training programs have evolved to include EUS and ERCP, hybrid procedures have evolved. Any future textbooks will have to include both procedures given their complementary nature. In addition to the advances made in these hybrid procedures, our focus should remain on clinical success and mitigating risk independent of technical success during a single procedure. This article will review the progress made since the last review in this journal[2] and clarify future research directions in the field.

INFECTION PREVENTION AND QUALITY IMPROVEMENT

Disposable duodenoscopes

While some practice changes in ERCP have been adopted because of an enthusiasm for technologic advance and the opportunity to treat complex problems, this past year was a somber reminder of our oath to do no harm. At no point in our history has there been a greater focus on infection prevention in health care with the ever-present threat of COVID-19. The prevention of transmissible infections has added cost and complexity to the reprocessing of duodenoscopes. Duodenoscopes have a complex design with intricate moving parts, long working channels, and are heat labile which make them difficult devices to disinfect[3]. Contaminated duodenoscopes have been implicated in the spread of multidrug resistant organisms[4-7]. Several measures have been taken to improve the disinfection process to mitigate cross contamination[8]. Along with this, the Food and Drug Administration (FDA) recommended a transition to a newer design of duodenoscopes with disposable components which can simplify the disinfection process[9]. This has also led to innovations in duodenoscope design

which include disposable parts and the development of a completely disposable duodenoscope.

Development of a single-use duodenoscope began in 2017. The challenge was manufacturing a scope comparable in performance and efficacy to a conventional reusable duodenoscope and eliminate the risk of any cross contamination[10]. Although there have been disposable bronchoscopes, nasopharyngoscopes, and ureteroscopes in clinical use, a disposable scope in gastroenterological clinical practice has been unprecedented[10]. In December 2019, the FDA cleared the first fully disposable duodenoscope – EXALT™ Model D Single-Use Duodenoscope (Figure 1), Boston Scientific Corporation (Marlborough, MA, United States)[11]. The endoscope has a 4.2 mm working channel, LED light, and conventional four-way steering. The current model D has a similar elevator lift angle and viewing angle when compared to the available reusable duodenoscopes. Subsequently in July 2020, a second disposable duodenoscope was cleared by the FDA-Duodenoscope model aScope™ Duodeno, Ambu A/S (Ballerup, Denmark)[5].

Advantages of a single-use duodenoscope are that they are sterile with no risk of cross contamination between patients. There is no need for disinfection or reprocessing, and it also eliminates the cost of maintenance and repair. Initial studies with the use of disposable duodenoscopes in a bench model, real patients, and a randomized study comparing with conventional duodenoscopes have shown equivalent performance characteristics compared to reusable duodenoscopes[10,12,13]. The significant disadvantages of the adoption of disposable duodenoscopes are the increased costs and increased environmental waste[14]. Further studies on the safety, efficacy, costs, patient outcomes, and environmental impact will help navigate the transition toward these novel devices.

Periprocedural management: Anesthesia involvement and propofol use in ERCP

ERCP has become safer with better equipment, standardized training programs, and better periprocedural care. As ERCP applications have broadened to include other modalities like EUS, there has been a significant increase in the use of involvement of anesthesia services in endoscopy. The safety of anesthesia-directed sedation in endoscopy is complex to analyze, but now better understood.

Safe sedation is a dynamic process that allows for technical and clinical success. In a United Kingdom study of therapeutic procedures, sedation was deemed inappropriate in up to 14% of cases[15]. Prior to Propofol use and general anesthesia, intolerance of sedation with discomfort was noted in one third to one half of ERCPs[16]. Comorbid patients with higher American Society of Anesthesiologist scores are more likely to have anesthesiologist involvement[17]. The safety of anesthesia service in endoscopy was analysed in a large cross-sectional study using the National Anesthesia Clinical Outcomes Registry. A total of 27721 patients had an ERCP performed with 12 deaths and 1052 anesthesia-related complications reported[17]. In the unadjusted model, ERCP was associated with an elevated odds ratio (OR) of 8.83 [95% confidence interval (CI): 7.70-10.12] relative to colonoscopy, that was not significant in the multivariate analysis.

Propofol is a sedative and hypnotic medication with a shorter duration of action compared to midazolam and fentanyl. Benefits of propofol include improvements in patient satisfaction, procedural outcome, and quicker recovery when compared to procedural sedation[18-20]. Propofol can cause significant hypotension and rapid respiratory depression. Further study was required to clarify propofol's safety in endoscopy. The ProSed 2 study[21] was a large multicenter prospective study reviewing sedation methods and associated complications of which 20967 procedures (6.7%) were ERCPs. The lowest rates of sedation-related complications were in patients receiving propofol monotherapy, and only 5 reported fatalities occurred during these ERCPs. An important point from the study is that their data collection focused on adverse events related to sedation alone, and delayed complications were not included. As with the Lieber study[17], delayed adverse events like post ERCP pancreatitis would not be captured by the author's study design[22]. Respiratory complications are more common in upper endoscopies[17], and the decision to intubate a patient remains individualized to the nature of the intended procedure and the patient's comorbidities. If anesthesia services are involved at our institution, any decision regarding the patient's anesthesia and intubation is collaborative with shared care decision making.

Future directions: Reducing post ERCP pancreatitis

Guidewire cannulation[23], pancreatic duct stents[24], intensive intravenous hydration [25,26], and rectal indomethacin[27] are used to reduce post ERCP pancreatitis[28]. In



Figure 1 The EXALT duodenoscope in use at our center.

the landmark trial published in the NEJM assessing the benefits indomethacin for post ERCP prophylaxis, more than 80% of patients also received a pancreatic duct stent [27]. The dose of rectal indomethacin used in the study was 100 mg. There was a reduction in post ERCP pancreatitis in both patients who received a stent (16.1% to 9.7% $P = 0.04$) and those who did not (20.6% to 6.3% $P = 0.049$). Post hoc analysis of this data suggested that the use of rectal indomethacin alone was better than a stent alone or the combination of stent and rectal indomethacin[29]. Despite data to support rectal indomethacin given before the procedure[30], and the double wire technique [31], the current state of practice remains individual to the practitioner. Side effects of long-term nonsteroidal anti-inflammatory drug use include renal impairment and peptic ulcer disease. A single dose of indomethacin did not result in a significant risk of acute renal impairment or clinically significant gastrointestinal bleeding[27]. The stent *vs* indomethacin for preventing post-ERCP pancreatitis (SVI) trial will clarify the value of a prophylactic pancreatic stent when added to rectally administered indomethacin[29] and should help further define standards of practice.

CANNULATION, BILIARY ACCESS, AND ALTERED ANATOMY

EUS assisted biliary access

Cannulation techniques have continued to evolve with advances in equipment[32]. Adding the EUS rendezvous may represent the last advance necessary to achieve 100% cannulation success during the index procedure. However, the additional risk of adding an EUS rendezvous to the index procedure needs to be evaluated prospectively in many centers. Failed cannulations are currently managed with a referral to interventional radiology for percutaneous transhepatic cholangiography (PTC). Biliary access and management would take the form of a combined PTC with ERCP, PTC with formation of an established tract, or antegrade stenting and stone removal[33]. EUS-guided rendezvous was first published in 2004[34]. Technical success has been reported with rates as high as 80% to 81%[35,36] with adverse event rates being 11%. A recent systematic review and meta-analysis reported a technical success of 86.1% (95%CI: 78.4-91) (12 studies reporting a total of 342 patients) and clinical success of 80.8% (95%CI: 64.1-90.8) (4 studies reporting a total of 94 patients)[37]. Consistent with previous reports, the pooled rate of adverse events was 14% (95%CI: 10.5-18.4) (12 studies; 42 events in 342 patients)[37]. At this time, the role of EUS rendezvous in ERCP is still not standardized and has not been compared to PTC in a comparative study[33]. In addition to EUS rendezvous, EUS directed transmural bile duct drainage is an alternate option. Transmural options for biliary drainage include hepaticogastrostomy (for proximal biliary obstruction) and choledochoduodenostomy (for distal biliary obstruction). While hepaticogastrostomy is performed using tubular metal stents, choledochoduodenostomy can be performed using tubular stents or LAMS based on bile duct size. A recent RCT compared EUS guided transmural biliary drainage *vs* ERCP for distal malignant obstruction and reported similar technical and clinical success[38].

Overtube-assisted enteroscopy and laparoscopic surgery-assisted ERCP

Given the burden of obesity and weight loss surgeries, expertise in altered surgical anatomy ERCP is necessary at tertiary referral centers. In a previous systematic review of overtube-assisted enteroscopy (OAE) and ERCP[39], patients with a Roux-en-Y with gastric bypass had a technically successful ERCP in just 70% of cases. Additionally, patients with a Roux-en-Y and either a hepaticojejunostomy (Figure 2) or pancreaticoduodenectomy undergoing ERCP had success in 76% of cases. A systematic review and meta-analysis[40] published in 2020 included 10 studies reporting a total of 398 procedures. The pooled rates of technical success of enteroscopy and OAE-ERCP were comparable at 75.3% (95%CI: 64.5-83.6) and 64.8% (95%CI: 53.1-74.9), respectively. The pooled rate of adverse events was 8.0% (95%CI: 5.2-12.2). The pooled rate of enteroscopy success with a double-balloon enteroscope in the 4 available studies was 83.5% (95%CI 68.3-92.2). Importantly, technical success of double-balloon enteroscopy ERCP (DBE-ERCP) was also higher at 72.5% (95%CI: 52.3-86.4). The pooled rate of adverse events with DBE-ERCP was 9.0% (95%CI: 5.4-14.5)[40].

Another approach to altered anatomy is the laparoscopic surgery-assisted ERCP [41]. At our institution, this surgery involves 4 Laparoscopic ports placed under direct visualization, formation of a gastrotomy, and placement of a rigid 19 mm sigmoidoscope into the gastrotomy. The duodenoscope is advanced through the sigmoidoscope, pylorus, and into the duodenum[42]. A meta-analysis in 2020 found that laparoscopic assisted surgery is significantly more effective than enteroscopy-assisted ERCP[43]. Therapeutic success was defined as completion of the diagnostic or therapeutic indication of the ERCP. The pooled proportion of patients with therapeutic success was higher in the surgery group at 97.9% (95%CI: 96.7-98.7) compared to 73.2% (95%CI: 62.5-82.6) in the enteroscopy-assisted ERCP patients. The benefits were countered by a higher rate of adverse events (19%; 95%CI: 12.6-26.4 *vs* 6.5%; 95%CI: 3.9-9.6) and a longer procedural time (158.5 min SD \pm 20 *vs* 100.5 min SD \pm 19.2 min).

EUS-directed transgastric ERCP

Given the challenges in managing patients with altered anatomy, EUS-directed transgastric ERCP (EDGE) is a novel way to approach patients with Roux-en-Y gastric bypass (RYGB)[44,45] and avoids the previously described laparoscopic-assisted access into the disconnected portion of the stomach. Importantly, the procedure has gained popularity since 2015[46] because of the ability to use conventional cannulation techniques and equipment. A retrospective multicenter review[47] of 178 patients reported a technical success of 98% (175/178) countered by 4 severe adverse events (SAE) (2.2%) and 10% of patients having a documented persistent fistula (9/90). It has been proposed that the EDGE could be used in patients with a RYGB, of which the details like limb length are unknown, and in patients with a surgically absent gallbladder[48]. A meta-analysis showed comparable rates of success to the laparoscopic assisted ERCP[45]. The significantly higher rates of technical success justify future comparative study of OAE and DBE ERCP with the EDGE procedure. The challenge for any prospective multicenter comparison will be that the EDGE can be done in 2 sessions[45]. The EUS placement of a transluminal stent, and then a second procedure at a follow-up interval to perform the ERCP. Although an EDGE procedure can be done at the time of LAMS placement, stent migration and free perforation can occur and most endoscopists wait 4-6 weeks prior to proceeding to ERCP.

ERCP AND ITS ROLE IN THE DIAGNOSIS AND MANAGEMENT OF BILIARY DISEASE

ERCP in complex bile duct stones

The main indication for ERCP is choledocholithiasis[49] which can cause cholangitis, biliary obstruction, and pancreatitis. For routine stones < 1 cm, a sphincterotomy with stone extraction using a balloon or basket is performed. Large bile duct stones present a particular challenge for safe and complete removal[50]. Recent guidelines have suggested performing a sphincterotomy and then a large balloon dilation over a sphincterotomy alone[51] for large stones. In a systematic review and meta-analysis, patients were more likely to have complete clearance of large stones (\geq 1 cm) OR 2.8, 95%CI: 1.4-5.7, I^2 26% if a balloon dilation was performed after a sphincterotomy (Figure 3).

Cholangioscopy is ideal for complex lithotripsy because of the ability to visualize the stone and introduce either a laser lithotripsy or electrohydraulic lithotripsy

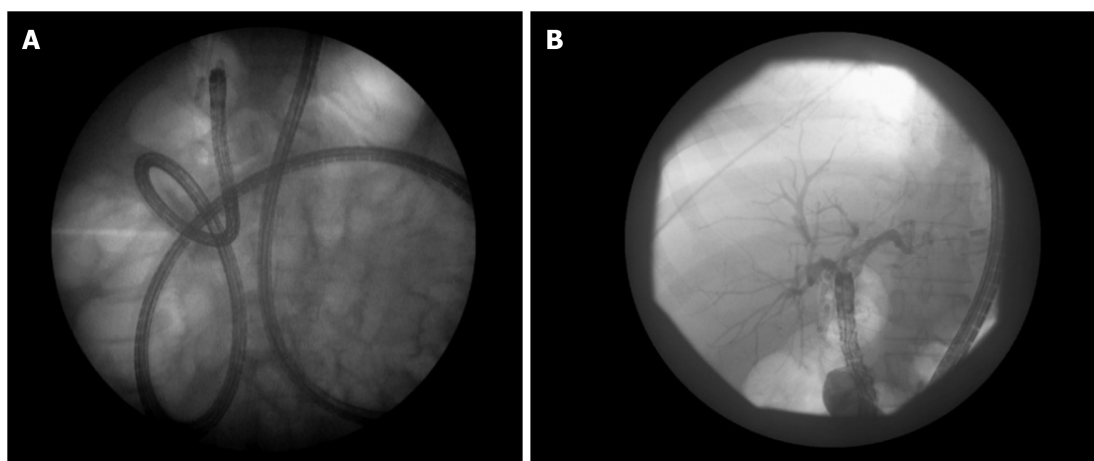


Figure 2 An overtube assisted enteroscopy and endoscopic retrograde cholangiopancreatography performed for a stent exchange and stone extraction. The patient had a Roux-en-Y hepaticojejunostomy after a bile duct injury. A: Stent exchange; B: Stone extraction.

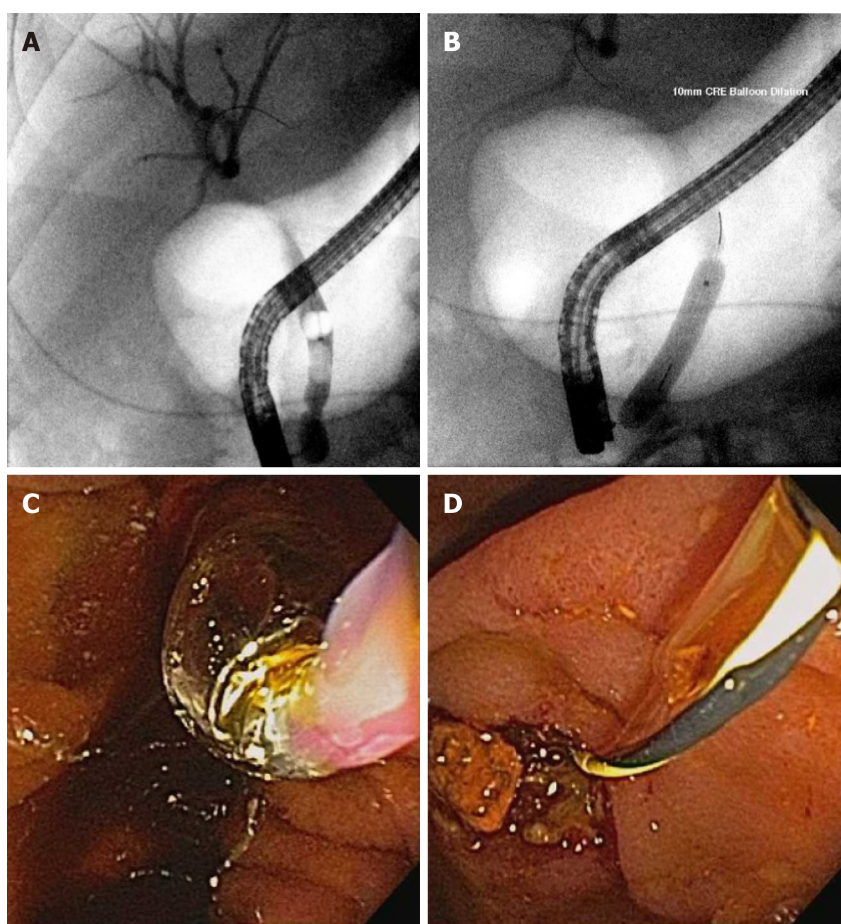


Figure 3 Large bile duct stone extraction. A: Bile duct stone; B-D: Balloon sphincteroplasty performed (B and C) with extracted stone fragment (D).

catheter[52]. Observational studies have reported procedural success in stone cases up to 92% with single operator cholangioscopy[53]. However, prior randomized controlled trials had not shown a significant difference between large balloon sphincteroplasty and cholangioscopy guided lithotripsy[54]. In a randomized comparison of large balloon sphincteroplasty with single-operator cholangioscopy guided lithotripsy, the proportion of ductal clearance was 72.7% and 93.9% in 1 session, respectively[55]. Treatment costs were higher in the cholangioscopy arm with no significant difference in complications. Future directions include standardized training in cholangioscopy and development of treatment algorithms for large bile duct stones[51].

ERCP in strictures and cholangiocarcinoma: Diagnosis and management

Cholangioscopy has progressed significantly since the transition from a dual-operator to a single-operator cholangioscope[52]. With the advent and proliferation of access to single-operator cholangioscopy, sensitivity for diagnosis of obstructive biliary pathology has improved. Cohort studies have shown adequate tissue for diagnostic assessment in 88% of patients with a biopsy performed with cholangioscopy[53]. A recent randomized multicenter trial confirmed higher first sample sensitivity with cholangioscopy compared to standard brushings (68.3% *vs* 21.4% $P < 0.01$) in patients with indeterminate biliary strictures[56]. Their data showed that the addition of the visual impression by digital single-operator cholangioscopy and direct biopsy had the highest likelihood of diagnosing malignancy in an indeterminate biliary stricture (Figure 4). For patients with primary sclerosing cholangitis, additional biopsies for fluorescence in situ hybridization (FISH) has been shown to improve sensitivity of indeterminate biliary strictures[57].

Management of unresectable cholangiocarcinoma has largely been limited to systemic chemotherapy and radiation. Currently, the main role of ERCP in cholangiocarcinoma is treating biliary obstructions with biliary stents. The advent of endoscopic options for unresectable cholangiocarcinoma has provided some hope in this field. Photodynamic therapy (PDT) and radiofrequency ablation (RFA) provide 2 available options for these patients. PDT works to ablate cancer tissue by using a photosensitizer that is activated by laser light. This results in tissue destruction by apoptosis and necrosis[58]. The main adverse event associated with PDT is photosensitivity. A sentinel study showed a survival benefit in patients receiving PDT [59]. A systematic review and meta-analysis published in 2017 by this journal[60] included 10 studies with 402 patients analyzed. The pooled OR for successful biliary drainage, defined as a reduction in bilirubin of 50% or greater at 7 d, was 4.39 (95%CI: 2.35-8.19) when comparing PDT and biliary stenting to biliary stenting alone. Future directions include targeted placement of the photosensitizer. Pullulan acetate-conjugated pheophorbide A is a photosensitizer that was successfully incorporated into self-expanding metal stent[61].

RFA is a local ablative therapy from a bipolar probe using high frequency current. A randomized trial from 2017 compared the outcomes of RFA with biliary stenting or biliary stenting alone[62]. The primary outcome of the study was mean survival time from the first RFA to time of death. In 21 months of follow-up, the mean survival time was significantly higher in the RFA and stent group (13.2 ± 0.6 mo) than if the patient received a biliary stent alone (8.3 ± 0.5 mo, $P < 0.001$). A previous retrospective comparative trial showed no difference between PDT and RFA in terms of survival rates[63]. Despite expected advances, the possible benefit of drug eluting stents remains untested in clinical trials. Vorinostat-eluting nanofiber membranes have showed antineoplastic effects against cholangiocarcinoma[64]. Stents with histone deacetylase inhibitors[65] and stents coated with gemcitabine and cisplatin have been fabricated[66], but neither have been tested in prospective studies.

PANCREATIC DISEASE: PANCREATIC STONES AND PANCREATIC LEAKS

ERCP in the management of pancreatic strictures

Radiological studies like CT and MRI/MRCP are the primary means of diagnosing chronic pancreatitis and strictures in 2021. However, in the early stages of chronic pancreatitis where the structural changes are limited, a combination of EUS, MRCP with secretin, and pancreatic function tests can be done in patients with high suspicion and risk factors[67]. ERCP is an important treatment option for patients with symptomatic chronic pancreatitis and strictures[68], with main pancreatic duct (MPD) strictures as the most likely to be intervened on. ERCP is recommended in patients with symptomatic, dominant strictures. These are defined as upstream MPD dilatation ≥ 6 mm in diameter, prevention of contrast medium outflow alongside a 6-Fr catheter inserted upstream from the stricture, or abdominal pain during continuous infusion of a nasopancreatic catheter inserted upstream from the stricture with 1 L saline over 12-24 h[69]. Stenting across the pancreatic duct stricture using ERCP decompresses the duct, helps relieve pain, and can result in improvement of exocrine pancreatic function [68]. Multiple studies have shown that stenting in chronic pancreatitis with strictures can improve pain[70-73]. A large multicenter study of more than 1000 patients followed up for a mean 4.9 years showed long-term success of endotherapy in 86% of

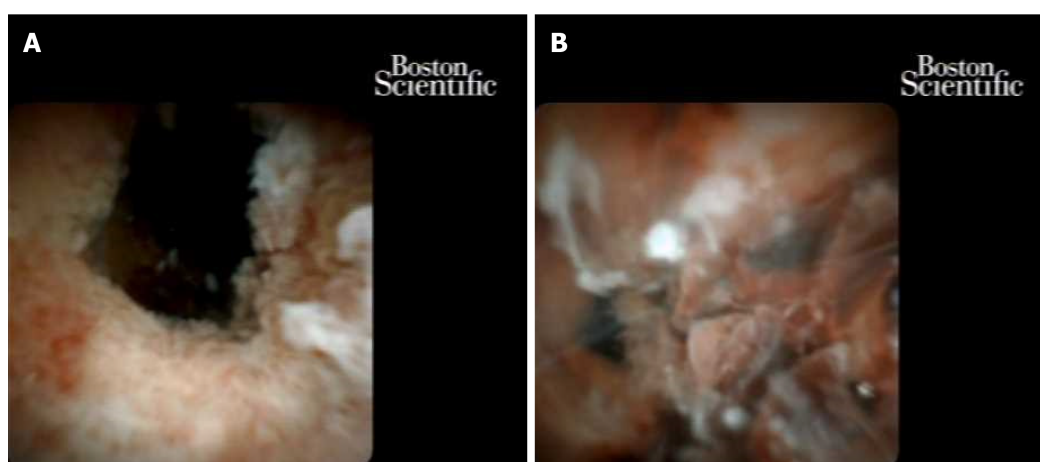


Figure 4 Cholangioscopy: Multifocal intraductal papillary neoplasm of bile ducts with high-grade dysplasia, that became cholangiocarcinoma. A: High-grade dysplasia; B: Cholangiocarcinoma.

patients but was lower at 65% in intention to treat analysis[68]. A large meta-analysis involving 16 studies and 1498 patients showed immediate pain relief in 88% and long-term pain relief in 67%. Complication rates for endotherapy were 7.85%[74]. More recently, rendezvous access using transgastric EUS puncture of the pancreatic duct and guidewire placement through a tight stenosis has allowed treatment of previously inaccessible strictures[75]. This is particularly effective in post Whipple patients with a stenotic pancreaticojejunostomy[76].

Commonly, a single plastic stent is used in pancreatic strictures. Multiple side-by-side plastic stents have also been used in treatment refractory strictures which did not respond to a single stent[77]. Newer stents like the fully covered self-expandable metal stents and a biodegradable noncovered self-expandable stents have been evaluated[78, 79]. Preliminary studies with longitudinal follow-up of fully covered self-expanding metal stents (FCSEMSs) in symptomatic main duct pancreatic strictures[79] are promising. In patients with MPD strictures that remained symptomatic after a single plastic stent who were treated with a 6 mm or 8 mm Niti-S Bumpt Stent (Taewoong Medical, Gimpo-SI, South Korea), 89% of patients were asymptomatic after 3 years. Given the technical success of FCSEMS[80] and relative safety[81,82], larger studies with long-term data will be performed. An ongoing trial will look at the degree of pain reduction, SAE, and stricture resolution[83] in patients who received a FCSEMS. To date, SEMS in the pancreatic duct in the United States remains investigational.

Pancreatotomy, pancreatic stones, and pancreatic leaks

The indications for pancreatoscopy include direct visualization of strictures, filling defects, and to differentiate benign from malignant intraductal pathology. Pancreatotomy can be helpful in the management of suspected intraductal papillary mucinous neoplasms as it can diagnose and stage the disease prior to surgical resection[84-86]. Per oral pancreatoscopy was first demonstrated in 1970s by Kawai *et al*[87], but required a second operator, and the technology was limited[88-90]. The first digital SpyGlass™ direct visualization cholangiopancreatroscope (Boston Scientific Corporation, Marlborough, MA, United States) was introduced in 2007. This included a working channel for biopsies and allowed for irrigation[91,92]. Further iterations had improved digital image quality[93]. The most recent digital version was launched in 2018 and has increased resolution, improved lighting, a retrieval basket, and a retrieval snare. The primary therapeutic indication of pancreatoscopy is direct lithotripsy for pancreatic duct stones[94]. Complication rates post pancreatoscopy have ranged from 3.8% to 12% and mainly include mild pancreatitis[85,95-97].

Chronic calcific pancreatitis is complicated by intraductal pancreatic stones which can be difficult to manage. In symptomatic patients, preprocedure imaging is mandatory to decide on adding extracorporeal shock wave lithotripsy (ESWL) before ERCP (Figure 5). ESWL is indicated if there are larger stones (≥ 5 mm) with ductal obstruction. Previous studies have shown that adding ESWL significantly decreases pain scores, yearly hospitalizations for pancreatitis, and opioid use[98]. A systematic review and meta-analyses of 22 ESWL ERCP studies noted high rates of complete stone fragmentation at 86.3% (95%CI: 76.0-94.0)[99]. The pooled percentage of patients with complete ductal clearance, however was 69.8% (95%CI: 63.8-75.5). This is a

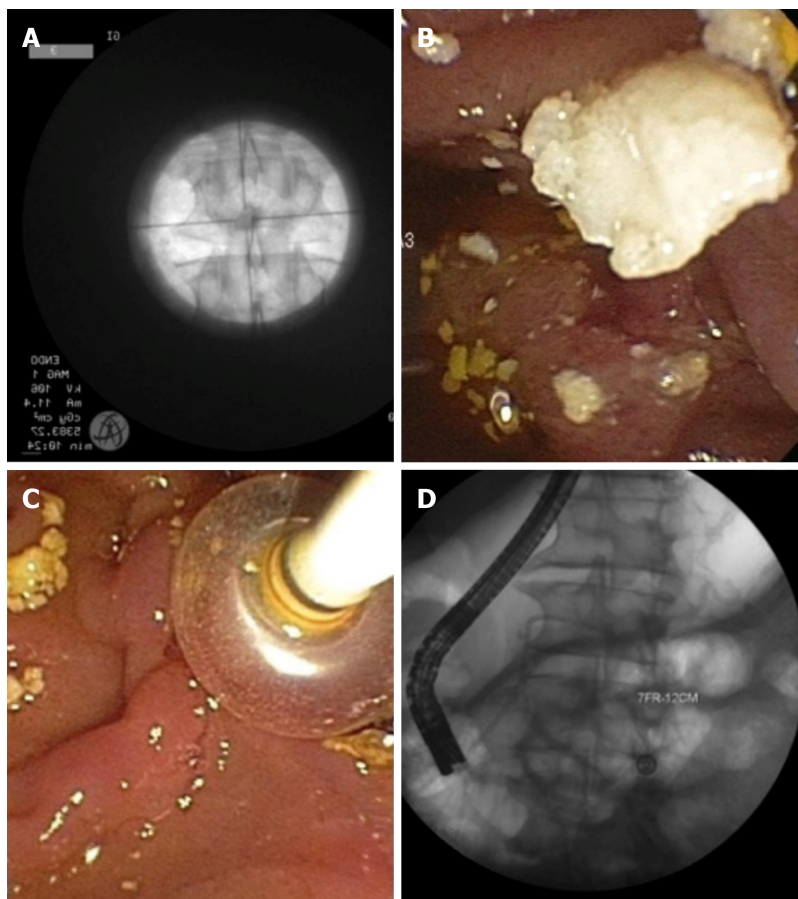


Figure 5 Chronic pancreatitis with a large pancreatic stone. A: Extracorporeal shock wave lithotripsy with stone; B and C: Successful stone extraction; D: Placement of a plastic pancreatic stent.

difficult patient population to manage and overall ESWL resulted in a moderate proportion of patients with complete absence of pain 64.2% (95%CI: 57.5-70.6). At our institution we perform an ESWL and ERCP in the same session (Figure 5). Repeat treatments are arranged based on post treatment symptom burden, interval imaging, and stone burden on repeat pancreatogram.

Pancreatic inflammation can cause a pancreatic duct leak with the unfortunate consequences of peripancreatic fluid collection, pseudocyst, walled-off pancreatic necrosis, pancreatic ascites, and fistula formation[100]. Management of pancreatic duct leaks historically involved conservative management including TPN and octreotide as a bridge to surgery. ERCP allows for diagnosis of the leak, transpapillary stent placement, and avoidance of surgery. Fluid collections from a pancreatic leak can be managed with internal luminal drainage and percutaneous drains[101,102]. Transluminal pigtail stents placed for pancreatic fluid leak in disconnected duct syndrome can be left in indefinitely as removing stents leads to risk of recurrent fluid collection[103].

CONCLUSION

ERCPs are done for multiple important reasons[1]. Although the most common indication remains choledocholithiasis with or without cholangitis[49], evolving indications include cholangiopancreatography with directed diagnostic and therapeutic procedures. Further training and improvements in practice have allowed for the use of over-tube, laparoscopic surgery-assisted, and EUS-facilitated ERCP[104] in patients who have undergone RYGB for morbid obesity. New developments in technology have allowed for the potential use of SEMS for refractory pancreatic duct strictures and the redesign of a duodenoscopes to include marketing of a disposable scopes to mitigate infectious complications from inadequately reprocessed devices. Despite the tumultuous last year and a half, there continues to be hope in the field of ERCP for managing complex disease.

ACKNOWLEDGEMENTS

Smith TD provided editing and administrative support in the production of this manuscript.

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Indications and outcomes of endoscopic resection for non-pedunculated colorectal lesions: A narrative review

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Author contributions: Shahini E conducted study conceptualization, drafting the manuscript, data collecting, and curation; Shahini E, Libânio D, Lo Secco G, Pisani A, and Arezzo A conducted paper editing; Arezzo A supervised; all the authors have critically reviewed the data entries for important intellectual content, checked for completeness of information, reviewed, and approved the final draft.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

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Abstract

In the last years, endoscopic techniques gained a crucial role in the treatment of colorectal flat lesions. At the same time, the importance of a reliable assessment of such lesions to predict the malignancy and the depth of invasion of the colonic wall emerged. The current unsolved dilemma about the endoscopic excision techniques concerns the necessity of a reliable submucosal invasive cancer assessment system that can stratify the risk of the post-procedural need for surgery. Accordingly, this narrative literature review aims to compare the available diagnostic strategies in predicting malignancy and to give a guide about the best techniques to employ. We performed a literature search using electronic databases (MEDLINE/PubMed, EMBASE, and Cochrane Library). We collected all articles about endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) registering the outcomes. Moreover, we analyzed all meta-analyses comparing EMR *vs* ESD outcomes for colorectal sessile or non-polypoid lesions of any size, preoperatively estimated as non-invasive. Seven meta-analysis studies, mainly Eastern, were included in the analysis comparing 124 studies and overall 22954 patients who underwent EMR and ESD procedures. Of these, eighty-two were retrospective, twenty-four perspective, nine case-control, and six cohorts, while three were randomized clinical trials. A total of 18118 EMR and 10379 ESD were completed for a whole of 28497 colorectal sessile or non-polypoid lesions > 5-10 mm in size. In conclusion, it is crucial to enhance the preoperative diagnostic workup, especially in deciding the most suitable endoscopic method for radical resection of flat colorectal lesions at risk of underlying malignancy. Additionally, the ESD necessitates further improvement because of the excessively time-consuming as well as the intraprocedural

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: April 27, 2021

Peer-review started: April 27, 2021

First decision: June 13, 2021

Revised: June 14, 2021

Accepted: July 9, 2021

Article in press: July 9, 2021

Published online: August 16, 2021

P-Reviewer: Ding L, Gao F, Rincon O

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Ma YJ



technical hindrances and related complications. We found a higher rate of *en bloc* resections and R0 for ESD than EMR for non-pedunculated colorectal lesions. Nevertheless, despite the lower local recurrence rates, ESD had greater perforation rates and needed lengthier procedural times. The prevailing risk for additional surgery in ESD rather than EMR for complications or oncologic reasons is still uncertain.

Key Words: Colorectal cancer; Adenoma detection; High-resolution colonoscopy; Chromoendoscopy; Pit pattern; Dysplasia

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Core Tip: The current unsolved dilemma concerns the necessity of a reliable submucosal invasive cancer assessment system, able to stratify the risk of the post-procedural need for surgery after endoscopic submucosal dissection of colorectal non-pedunculated lesions. It should be capable of selecting the at-risk subgroups of patients in whom endoscopic submucosal dissection could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy according to current endoscopic technology, to choose wisely among endoscopic mucosal resection, and endoscopic submucosal dissection procedures.

Citation: Shahini E, Libânio D, Lo Secco G, Pisani A, Arezzo A. Indications and outcomes of endoscopic resection for non-pedunculated colorectal lesions: A narrative review. *World J Gastrointest Endosc* 2021; 13(8): 275-295

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/275.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.275>

INTRODUCTION

The Japanese[1,2], European[3], and American[4,5] guidelines recommend that large sessile colorectal polyps and laterally spreading tumor (LST) can be successfully removed by piecemeal endoscopic mucosal resection (p-EMR)[2,3,5,6] if there are no signs of deep submucosal invasion on endoscopic assessment[5-9].

EMR is fast and safe to remove non-pedunculated colorectal lesions sized above 10-15 mm[1-3,5]. However, p-EMR may impair accurate histological assessment and has higher recurrence rates than *en bloc* resection[1-3,5], resulting in a higher frequency of post-procedural surgery[1-3,5].

En bloc EMR (with distinct techniques) for sessile polyps or LSTs ≥ 20 mm has been reported in 16%-48% of cases[10-14], with a success rate ranging from 42.9% to 98.8% and R0 rate between 45.0% to 96.7% cases[15-19]. A 2009 meta-analysis about endoscopic excision of large colorectal sessile polyps and LST lesions, reported an *en bloc* EMR rate of 62.85% and R0 rate of 58.66% on a sample of over 5221 patients[20]. It would be adequate to refer to the recurrence and surgery rates for EMR. Nevertheless, EMR is contraindicated in the presence of signs of deep invasion, like tissue ulceration/hardening, central depression, and non-lifting signs after submucosal injection[1-3,5].

Endoscopic submucosal dissection (ESD) should be preferred over EMR in cases of colorectal lesions greater than 20 mm with signs of superficial submucosal invasive cancer (SMIC), non-granular (NG) surface pattern, or when it could not be radically removed by the conventional procedures[2,5,21].

ESD achieves higher rates of *en bloc* and R0 resection, which translates into more adequate histological assessment and lower rates of local recurrence[1,2,5,22]. The downsides of ESD are longer procedural time and higher intraprocedural complications such as perforation, which of course are lowered by experience[1,2,5,21]. However, a recent systematic review has suggested limiting the indication for ESD because of the high incidence registered of non-curative resection due to a wrong SMIC assessment[2].

Colorectal lesion morphology can predict the risk of SMIC and help to guide the most appropriate endoscopic treatment[3,5,21,23]. Three parameters have to be considered: morphological pattern (MP) according to the Paris 2002 classification[24] and updated for the colon in the Kyoto 2008[25]; glandular pattern [pit pattern (PP)] according to the Kudo classification[26]; and vascular pattern[24,25,27-29]. The assessment of MP requires the use of a high-definition endoscope[21,24,25,27].

Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their MP, as well as to Kudo PP, narrow-band imaging (NBI) international colorectal endoscopic (NICE), and Japanese NBI Expert Team (JNET) classifications are described in Table 1[6].

Regarding MP, Paris type 0-IIc non-polypoid lesions have a higher risk of SMIC than Paris 0-IIa, 0-IIb, and polypoid lesions[5,21,24,25,27]. Furthermore, the rates of SMIC for granular (G) homogenous, G nodular mixed, NG flat, and NG pseudodepressed LSTs were 4.9%, 15.9%, 3.0%, and 19.4%, respectively[30]. Additionally, the risk of occult SMIC according to colonic lesion morphology and location have been estimated to be 0.8% for 0-IIa G (proximal: 0.7%, distal: 1.2%), 7.1% for 0-IIa + Is G (proximal: 4.2%, distal: 10.1%), 3.7% for 0-Is G (proximal: 2.3%, distal: 5.7%), whereas SMIC risk was 4.2% for 0-IIa NG (proximal: 3.8%, distal: 6.4%), 14.1% for 0-IIa + Is NG (proximal: 12.7%, distal: 15.9%), 15.3% for 0-Is NG (proximal: 12.3%, distal: 21.4%)[6]. Though those lesions without these features might still contain SMIC that is not visible on endoscopic inspection, which is defined as covert SMIC[6].

Current guidelines support the use of high-resolution colonoscopy with chromoendoscopy (dye or virtual) and optical magnification to establish the presence of SMIC and the feasibility of resection[24,25,26,31,32]. Virtual chromoendoscopy, by “real-time imaging” modifications (with NBI, flexible spectral imaging color enhancement, or i-Scan), allows the correct evaluation of PP and vascular pattern[5,21,24-26]. Optical magnification endoscopes identify the mucosal surface PP according to the Kudo classification[2,33].

The Japanese usually assess the risk of colorectal lesion infiltration by using chromoendoscopy with indigo carmine or crystal violet. In the Western areas, the reduced spread of magnification (both high costs and long procedural times) has restricted the evaluation of the risk of lesion infiltration to lifting-sign[3,21,26,34].

These techniques have improved the early detection of colorectal cancer (CRC) by characterizing the microscopic appearance of the dimples or furrows that separate the mucosal cells, which change according to the distinct stages of dysplasia and neoplastic transformation[5,21,24,26,34]. Specifically, the sensitivity and specificity for the diagnosis of T1 CRC with deep SMIC by using NBI were 79% and 94%, respectively[35].

NICE CLASSIFICATION

The employment of NBI[36,37] has led to NICE classification[38] that distinguishes among hyperplastic polyps (type 1), adenomas (type 2) with/without superficial SMIC, and cancers with deep SMIC (type 3) based on color features, vessels, and surface pattern[38-40].

Therefore, lesions with glandular distortion but intact vascular structures [Kudo Vi, NICE type 2] are at risk of a superficial SMIC and are suitable for endoscopic *en bloc* resection. Whereas a highly distorted PP or an absence/irregularity of the submucosal vessels (Kudo Vn or NICE type 3) are strongly predictive of deep SMIC. Therefore, after performing biopsies and tattoos of the lesion, surgical treatment should be judged[38].

The sensitivity, specificity, positive predictive value, and negative predictive value of the NICE classification for predicting deep SMIC were 58.4% (95% confidence interval (CI): 47.5%-68.8%), 96.4% (95%CI: 95.5%-97.2%), 41.6%, (95%CI: 32.9%-50.8%), and 98.1% (95%CI: 97.5%-98.7%), respectively[39], whereas 99.1%, 57.7%, 95.4%, and 88.2%, respectively in differentiating neoplastic from non-neoplastic polyps[40]. Interobserver agreement was relevant (kappa: 0.70) for predicting deep SMIC[41]. Also, the sensitivity for the diagnosis of deep SMIC regarding lesions with type 3 of NICE was significantly greater among very expert endoscopists than in the less-experienced ones (91.7% *vs* 83.3%; *P* = 0.04)[42].

Table 1 Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their morphological pattern as well as to Kudo pit pattern, narrow-band imaging international colorectal endoscopic, and Japan narrow-band imaging expert team classifications

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
Morphological pattern¹					
0-IIa G	5.7%	70.0%	1.7%	89.1%	64.6%
0-Is G	11.5%	83.2%	5.8%	91.2%	77.3%
0-IIa + Is G	22.9%	77.4%	8.4%	91.7%	72.8%
0-IIa NG	27.4%	79.5%	10.8%	92.4%	75.2%
0-Is NG	16.6%	95.5%	25.0%	92.7%	89.0%
0-IIa + Is NG	15.9%	94.5%	20.7%	92.6%	88.0%
Kudo pit pattern (NBI)²	73.3%-93.7% ³	89.2%-100% ³	93.7%-100% ³	89.2%-96.4% ³	92.0%-96.7% ³
NICE classification⁴					
Type 1	82.1%-84.6%	93.8%-94.9%	65.9%-92.5%	60.4%-98.2%	93.9%-97.8%
Type 2	89.8%-91.4%	84.3%-86.3%	89.1%-90.7%	97.3%-97.7%	56.6%-61.2%
Type 3	83.3%-91.7%	96.4%-97.0%	96.0%-96.8%	45.8%-54.0%	99.4%-99.7%
JNET classification⁵					
Type 1	73.0%-87.1%	96.0%-99.5%	73.4%-92.3%	96%-98.9%	93.0%-98.5%
Type 2A	82.5%-96.0%	70.0%-91.1%	90.3%-96.7%	62.1%-92.1%	84.5%-90.9%
Type 2B	42.0%-75.6%	84.2%-95.0%	26.0%-67.3%	92.2%-98.0%	81.3%-93.0%
Type 3	35.0%-91.7%	98.1%-100%	63.2%-100%	93.8%-99.7%	94.0%-98.0%

¹Diagnostic performance of lesion classification types according to Paris classification for covert submucosal invasive cancer (SMIC) (SMIC that is not visible on endoscopic inspection).

²Narrow-band imaging.

³These percentages refer to the ability of preoperative magnifying chromoendoscopy (Kudo pit pattern classification by narrow-band imaging assessment of mucosal surface) to predict depth of submucosal invasion for large colorectal lesions.

⁴Narrow-band imaging international colorectal endoscopic (NICE) classification, NICE type 1: hyperplastic polyps, NICE type 2: adenomas (with/without risk of a superficial SMIC), NICE type 3: strongly predictive of cancers with deep SMIC.

⁵Japan narrow-band imaging expert team classification (JNET), JNET type 1: predictive of hyperplastic/sessile serrated polyps, JNET type 2A: predictive of neoplasia with low/high-grade intramucosal neoplasia, JNET type 2B: predictive of high-grade intramucosal neoplasia/shallow submucosal invasive cancer, JNET type 3: predictive of cancer with deep SMIC. PPV: Positive predictive value; NPV: Negative predictive value; NBI: Narrow-band imaging; JNET: Japan Narrow-band imaging expert team classification; NICE: Narrow-band imaging international colorectal endoscopic; NG: Non-granular; G: Granular.

JNET CLASSIFICATION

The JNET classification consists of four categories and uses vascular pattern and MP to diagnose hyperplastic/sessile serrated polyps (type 1), neoplasia with low/high-grade intramucosal neoplasia (type 2A), high-grade intramucosal neoplasia/shallow SMIC (type 2B), and cancer with deep SMIC (type 3)[42-46]. The interobserver and the intraobserver agreement for the JNET classification were moderate (kappa: 0.52) and excellent (kappa: 0.88), respectively. Type 2B lesions included a variety of colorectal tumors, including those with high-grade dysplasia, with superficial and deep SMIC [45]. Both non-expert/expert endoscopists had similar specificity, negative predictive value, and accuracy (> 90%) for 1/2B/3 types and sensitivity and positive predictive value above 90% for type 2A, whereas type 2B exhibited a sensitivity of only 42%[44].

Colorectal polyps exhibiting ulceration, excavation, defined deep depression, Paris IIc and IIa+c, mucosal friability, convergent plicae, and Kudo type V PP most likely correspond to SMIC. Therefore, they are at high risk for lymphovascular invasion and lymph node metastasis[48-52].

Additionally, superficial SMIC (sm1 and sm2, involving the upper and middle level of the submucosa, respectively)[25] was not closely associated with non-lifting signs because underlying undamaged submucosa may still expand, unlike deep SMIC (sm3, involving the lower level of the submucosa)[25,53-55]. Accordingly, when deep SMIC

is suspected or proven, in addition to excision of the lesion, the removal of the loco-regional lymph nodes is necessary, which can only be achieved by surgery[5,21,26,25,52].

Moreover, staging even with echoendoscopy and magnetic resonance imaging can be considered for rectal tumors with endoscopic features suspected for SMIC and eventually lymph node staging[56,57]. Colorectal surgery is recommended for lymphovascular invasion, SMIC deeper than sm1, positive/non-evaluable vertical margins, or poorly differentiated tumor[8,21,26,24,25]. When a positivity of horizontal margin is shown without additional high-risk criteria, endoscopic surveillance/re-treatment could be weighed instead of surgery[21,26,24,25].

EMR en bloc or piecemeal: indications, efficacy, and safety

On the other hand, colorectal lesions without SMIC-suggestive features have a high likelihood of being radically removed by endoscopic techniques and should not be referred for surgery without primary estimating the possibility of a polypectomy/EMR at an expert endoscopy center[58]. Moreover, it should be avoided to perform biopsies in such lesions because it can produce submucosal fibrosis, not allowing the lifting process[5,21,25,26,34]. Indeed, in a study[59] of 36 patients with 38 large polypoid lesions, negative for cancer who were referred from a colorectal surgeon to an EMR expert, 79% of the lesions were successfully treated endoscopically, thus avoiding unnecessary surgery in 71% of cases.

EMR encompasses different techniques (*i.e.* inject and cut, with either cold or hot snare; cap-assisted; underwater; hybrid)[32,60-63]. Various studies have proved that *en bloc* or p-EMR can radically and safely remove most colorectal sessile or non-polypoid lesions[13-16,64].

En bloc or p-EMR resections aim particularly at a resection with a histologically confirmed negative resection margin. Particularly, *en bloc* R0 resection, together with the absence of undifferentiated adenocarcinoma, deep invasion (submucosal invasion > 1000 μ m), and lymphovascular invasion excludes the risk of lymph node metastasis [2,3,5,7,8,10-16,52,64].

Specifically, *en bloc* EMR has been reached in 47.2%[15], 53.5%[11], 66.3%[14], 91.3%[17], and 98.8%[16] of procedures, whereas R0 was achieved in 45%[14], 88.9%[15], 89.2%[10], 91.0%[11], and 96.7%[18] of events for colorectal sessile polyps and/or LSTs [14,15,17,18] or for recurrent adenomas after p-EMR[11] of various diameters ($\geq 10/20$ mm[10,14,17], ranging 8-100 mm[11], 10-50 mm[18], or 20-50 mm[14]).

According to current guidelines, p-EMR is mainly employed for treating large non-malignant colorectal sessile or non-polypoid lesions[3,63,65]. To be optimally performed, it requires the resection to be completed by a limited number of pieces and adequate margins[2,3,5].

However, according to a meta-analysis published in 2016[65] including 6442 patients and 6779 large colorectal polyps, successful endoscopic resection (independently from surgery following endoscopy and, in some events, to histology) by any endoscopic technique, post-endoscopic resection bleeding, perforation, and mortality occurred in 96.3% (95%CI: 96.0%-97.0%), 6.5% (95%CI: 5.9%-7.1%), 1.5% (95%CI: 1.2%-1.7%), and 0.08% cases (95%CI: 0.01%-0.15%), respectively, after resection. A rate of 8% of patients (95%CI: 7%-10%, $I^2 = 78.6\%$) underwent surgery due to non-curative endoscopic resection and 1.0% (95%CI: 0.7%-1.4%, $I^2 = 0\%$) due to adverse events[65].

Other studies have also reported various percentages of post-EMR bleeding in 0% [14,16,19], 1.75% [18], 2.8%-3.1% [13], 6.2% [66], 9.8% [11], and 10.8% [12] after the resection of large colorectal lesions.

The efficacy and safety of hot and cold snare EMR for non-pedunculated colorectal adenomas < 20 mm has been evaluated in few studies, which suggested a capacity for resectability improvement and for delivering better histopathological evaluation especially with the cold snare technique[15,67-69].

Besides, a Japanese single-armed multicenter prospective trial[67] of 624 patients undergoing standard EMR of non-pedunculated polyps with a diameter ≤ 20 mm, successful *en bloc* and R0 resection rates of 93.3% and 78.3%, respectively, were observed. Postoperative rates of bleeding and perforation were 1.1% and 0%, respectively[67].

Another Japanese multicenter randomized controlled trial (Yamashina *et al*[68], 2019) showed for 102 sessile lesions ranging between 10-20 mm and treated by standard EMR (with electrocautery) an *en bloc* resection of 75% (95%CI: 65%-83%), R0 resection of 50% (95%CI: 40%-60%), with a median procedure time of 175 s, and adverse events were reported in 2% of cases.

A Japanese prospective, observational study[69] assessing an overall 80 non-pedunculated adenomas measuring 10-14 mm and treated with cold snare EMR

reported *en bloc* and R0 resection rates of 82.5% and 63.8%, respectively. No post-procedural adverse events occurred.

Otherwise, in a retrospective, single-center study[15] analyzing 44 EMR salvage procedures (following the previous p-EMR) of polyps whose median size was 14 mm, *en bloc* resection rate was 15.9%, R0 resection rate was 31.8%, and intraprocedural argon plasma coagulation (APC) ablation of visible residual was 65.9%. Bleeding occurred in 4.5%, and there were no perforation events[15].

Among the studies evaluating EMR for colorectal lesions < 20 mm, the majority did not analyze the recurrence rates[67-69], but only one reported a 39.4% of recurrence at surveillance[15].

Hot snare EMR is the conventional technique employed for resection of large (≥ 20 mm) non-malignant sessile colonic polyps, although severe adverse events can occur mainly due to electrocautery application.

Cold snare p-EMR of sessile colonic polyps or LSTs ≥ 20 mm represents an alternative technique feasible, efficient, and secure in many cases, although large randomized/prospective trials to strengthen the results and to define which polyps are rightly suitable for this method are needed. Furthermore, the adverse event and polyp recurrence rates are usually low.

A retrospective study[70] reported similar technical success for both cold snare p-EMR and standard EMR employed for 156 and 406 sessile serrated lesions sized ≥ 20 mm (100% *vs* 99%; P = not significant), respectively. While cold snare p-EMR was not associated with adverse events, delayed bleeding and deep mural injury were observed in 5.1% and 3.4%, respectively, following EMR[70].

A retrospective Australian study[71] of 186 patients treated by cold snare p-EMR for 204 sessile polyps ≥ 20 mm reached a median interval of 150 d of residual/recurrent polyp in 5.5% of cases, whereas at a median interval-time of 18 mo registered a 3.5% late residual/recurrent polyp. Bleeding occurred throughout the p-EMR in 2.2% of cases, whereas post-EMR bleeding occurred in 3.8%[71].

In a prospective observational cohort study[72], the risk of residual or recurring adenoma after p-EMR of large non-pedunculated polyps was 10.8% (mean size, 31.6 ± 10.1 mm)[72].

A prospective and multicenter Australian study[73] on 1178 LSTs ≥ 20 mm removed by p-EMR showed a recurrence rate of 19.4%[73]. In detail, LST size ≥ 40 mm [odds ratio (OR) = 2.47; $P < 0.001$], the intraprocedural bleeding (OR = 1.78; $P = 0.024$), and high-grade dysplasia (OR = 1.72; $P = 0.029$) were independent predictors for polyp recurrence[73].

Indications, outcomes, and adverse events of underwater EMR

Principal boundaries with conventional EMR involve high percentages of polyp recurrence and low *en bloc* resection rates, especially for lesions sized above 20 mm. Underwater EMR (U-EMR) represents an alternative method for *en bloc* resection of more extensive lesions. Comparison studies showed the feasibility and safety of U-EMR that is associated with higher *en bloc* and R0 resection rates for colonic lesions compared to standard EMR[62].

Previously, Binmoeller *et al*[13], in a prospective observational study, reported a 100% R0 resection concerning U-EMR for large sessile polyps, and delayed bleeding occurred in 5%[13].

In a multicenter randomized controlled trial[68], U-EMR for polyps with intermediate-size (10-20 mm in diameter) demonstrated higher *en bloc* and R0 resection rates as compared to conventional EMR [89% (95%CI: 81%-94%) *vs* 75% (95%CI: 65%-83%), $P = 0.007$; and 69% (95%CI: 59%-77%), *vs* 50% (95%CI: 40%-60%), $P = 0.011$, respectively]. There was no significant difference in prevalence of adverse events in the U-EMR group (2.8% *vs* 2.0%, P = not significant)[68].

In a meta-analysis of American and European studies[74], the U-EMR technique exhibited an R0 resection rate of 96.36% (95%CI: 91.77%-98.44%). Also, *en bloc* resection rate was described in 57.07% (95%CI: 43.20%-69.91%) for sessile polyps and non-polypoid lesions (mean size range, 15.0-33.8 mm). Adverse events occurred in 3.31% (95%CI: 1.97%-5.52%) and late bleedings in 2.85% (95%CI: 1.64-4.90%), in the absence of perforation[74].

In a recent systematic review and meta-analysis[75], U-EMR has shown a higher *en bloc* resection rate than conventional EMR for removing polyps > 20 mm in size (OR = 1.9; 95%CI: 1.0-3.5; $P = 0.04$), whereas R0 resection (OR = 3.1; 95%CI: 0.7%-12.6%; $P = 0.14$), piecemeal resection (OR = 3.1; 95%CI: 0.7%-12.6%; $P = 0.13$), and diagnostic accuracy for CRC (OR = 1.1; 95%CI: 0.6%-1.8%; $P = 0.82$) were similar. There were lower rates of recurrence (OR = 0.3; 95%CI: 0.1%-0.8%; $P = 0.01$) and incomplete resection (OR = 0.4; 95%CI: 0.2%-0.5%; $P = 0.001$) with U-EMR. The two methods

produced equivalent procedural times and safety profiles.

Indications and outcomes of cap-assisted EMR and EMR with a ligation device

The cap-assisted EMR (C-EMR) and EMR with a ligation device (EMR-L) in the colon have limited indications, especially for R0 resection of small rectal neuroendocrine tumors (NETs) because their radical removal can be difficult to achieve with standard endoscopic resection techniques due to the frequent involvement of the submucosal layer[76,77].

Some articles have described the usefulness of a distally attached cap during colonoscopy for shortening cecal intubation, decreasing patient discomfort, improving adenoma detection rate, and simplifying mucosal resection of non-pedunculated lesions[81-85]. Moreover, C-EMR can resect more adequately complex and large inter-plicae non-polypoid lesions, especially those located in the right colon[18].

A 2011 single-center prospective, randomized, controlled trial[86] showed during C-EMR/colonoscopy of 166 patients a significantly reduced procedural time (3.5 ± 4.5 vs 4.2 ± 5.1 min, $P = 0.010$), a higher polyp detection rate (3.4 ± 2.7 vs 2.7 ± 1.9 , $P = 0.003$), and a lower rate of missed polyps (1.1 ± 1.5 vs 0.8 ± 0.9 , $P = 0.024$) than patients undergoing conventional colonoscopy[86].

As reported in a retrospective study[87], C-EMR was feasible for resection of small rectal NETs. This study analyzed a total of 34 rectal NETs that were removed by C-EMR, reaching a higher R0 resection rate (94.1% vs 76.8% , $P = 0.032$) and a higher tendency of frequency of intraprocedural bleeding (8.8% vs 0% , $P = 0.051$) than standard EMR ($n = 56$); the procedural time was significantly shorter in the C-EMR group (3.9 ± 1.1 vs 19.0 ± 12.1 min, $P < 0.001$) than the ESD group ($n = 32$)[87]. For NETs ranging 6-8 mm in size, there were no differences in the adverse events or R0 resection rates between the C-EMR group and ESD group.

A review[88] suggested that C-EMR is effective and safe when polyp removal is challenging *via* standard EMR technique. Specifically, this study described a rate of 100% R0 resection after C-EMR of 21 ileocecal valve polyps (median size, 15 mm), and late bleeding occurred in 4.8%[88].

On the other hand, a Japanese and retrospective study[89] evaluating 22 colorectal carcinoid tumors (mean size, 6.2 mm) that were treated by EMR-L reported *en bloc* and R0 resection rates of 73% and 50%, respectively, for EMR-L. Perforation and bleeding did not occur[89].

Finally, the authors of a recent retrospective Korean study[90] deduced that EMR-L may be the preferred treatment method for small rectal NETs, considering the higher *en bloc* resection rate in the EMR-L group than C-EMR one (100% vs 92.9% , $P = 0.003$). Though only a superior trend for R0 resection rate was observed in the former group (92.5% vs 83.3% , $P = 0.087$), and there were no differences in intraprocedural adverse events ($P = 0.870$)[90].

Risk factors for adverse outcomes and recurrences after EMR of colorectal lesions > 20 mm

The factors that limit EMR[91] are resection technique[92,93], polyp size[94,95], previous removal attempts[96], location[97], endoscopist experience, and patient comorbidities[91,95,96,97].

Indeed, the risk factors for post-procedural hemorrhage included polyp location in the proximal tract[66,98,99,100] and particularly those larger than 40 mm[101,102]. Perforation occurred unusually (0.36% - 6.30%)[12-14,98,103] and was higher particularly for lesions of the transverse colon with underlying high-grade dysplasia, SMIC, and after *en bloc* resection[3].

In detail, the perforation event has complicated endoscopic procedures in 0%[12, 13], 0.36%[11], 1.4%-1.5%[98,103], 1.75%[18], 1.5%-1.9%[16], 2.9%[19], and 6.3%[14] of cases, with a negligible procedure-related fatality ($< 0.1\%$)[12-14,18,19]. Late bleeding was usually endoscopically managed, while prophylactic coagulation of visible vessels or clip use did not lessen the risk of bleeding[1,3,6,50].

Also, complex lesions located at the ileocecal valve (single and both lips) were associated with resection failures (OR = 12.2; 95%CI: 1.64%-90.50%; $P = 0.002$) as well as in cases of terminal ileal involvement (OR = 121.3; 95%CI: 1.52%-84.00%; $P = 0.002$)[97]. The appendiceal orifice, the anorectal junction, and the peridiverticular sites have also been considered challenging to remove the lesions safely[2,3,5,10,98].

Additionally, an American study identified the previous resection attempts as a significant risk factor for failure of complete excision (OR = 0.024; $P = 0.001$) and for achieving a successful resection without applying thermal ablation of residual (OR = 0.081; $P < 0.001$)[96].

Moreover, no study has defined the threshold extent for which *en bloc* EMR is unsafe. *En bloc* EMR is generally limited to lesions sized up to 20 mm, while the larger usually require ESD or surgery for local radicality[5,7,21,20,32]. Specifically, for sessile polyps and flat lesions, the maximum size to perform safely *en bloc* excision was 15-20 mm proximal to the splenic flexure where the risk of perforation is the greatest and 20-25 mm in the sigmoid/rectum tract for anatomic reasons[3,5,20,32].

Interestingly, the circumferential incision of lesions with hybrid ESD methods (*i.e.* cap-assisted or pre-cut-EMR) can allow the extension of the size threshold for complete resection while reducing the risk of perforation[19,99,104,105].

Hence, the cases including sessile colorectal polyps ≥ 20 mm (Paris classification 0-IIa, 0-Is, 0-Isp), LSTs, lesions located in difficult areas, or colitis-associated dysplasia have been judged amenable to be referred to experienced endoscopists in a high volume tertiary referral center before surgical option[2,3,5,11].

The EMR treatment for large colorectal sessile or non-polypoid lesions is associated with heterogeneous rates of adenoma recurrence/persistence that range between 0% and 39.4%[74,106-108], depending on the EMR technique (*i.e.* standard, hybrid, cap-assisted, or underwater), polyp size/histology, a higher number of resected pieces, previous attempts of resection, and surveillance period (3-6 mo or ≥ 12 mo)[19,61,63,96,109].

Recurrence rates succeeding cold snare p-EMR were similar to standard EMR at two consecutive surveillances (4.3%/2.0% *vs* 4.6%/1.2%, respectively)[70].

Previously, Kikuchi *et al*[106] evaluated the risk of recurrence even in patients with CRC and SMIC of any size following EMR; none of the 17 patients with superficial SMIC registered localized recurrence or lymph node metastases.

Bergmann and Beger[18] showed a 3.3% local recurrence after treating lesions with sizes ranging from 10-50 mm. Notably, Masci *et al*[16] described an approximately 15% recurrence rate of the lesions either in high- or low-volume centers.

Specifically, a meta-analysis[65] including 6442 patients treated with endoscopic resection of 6779 large polyps found an endoscopic recurrence in 13.8% of cases.

Moss *et al*[17], Conio *et al*[12], and Buchner *et al*[11] showed adenomatous recurrence at the resection site in 16%, 21.9%, and 27%, respectively, for large sessile polyps or LST lesions, referred to using EMR.

Pohl *et al*[109] reported a 17.3% incomplete resection by using hot snare EMR for large lesions. On the other hand, Thoguluva *et al*[64] observed after cold snare EMR of intermediate-size non-polypoid lesions an overall residual disease in 4.1%, whereas Muniraj *et al*[63] reported 20% of recurrences at 6 mo. Additionally, Rex *et al*[108] displayed a comparable residual polyp rate after the EMR of large sessile serrated adenoma/polyps or traditional adenomas (8.7% *vs* 11.1%, respectively).

Non-standard EMR techniques have reported favorable outcomes regarding reducing residual or recurrence lesions[15,74,87,107]. Indeed, Hong *et al*[14], reported no recurrence after EMR with circumferential incision for the treatment of large sessile polyps and LSTs. Yang *et al*[87] observed no recurrence in the C-EMR group after resection of 34 small rectal NETs. Binmoeller *et al*[13] and Spadaccini *et al*[74] showed a recurrence rate of 1.8% and 8.8%, respectively, using U-EMR for sessile polyps and non-polypoid lesions at surveillance program. In contrast, Kim *et al*[15] displayed a significantly lower recurrence in the U-EMR group than the standard EMR (10.0% *vs* 39.4%). Instead, a 4% recurrence was described after the employment of C-EMR for sessile lesions (or LSTs) over 1 year of surveillance[107].

P-EMR has been judged as an independent risk factor for recurrence after endoscopic resection of non-pedunculated colorectal adenomas and early carcinomas [110].

In detail, Kim *et al*[111] observed at surveillance following the previous p-EMR of large non-pedunculated adenomas, a second and third recurrence in 34% and 20% among 70 recurrent lesions, respectively. Nevertheless, another study[19] recorded a surprisingly higher recurrence rate for standard EMR than p-EMR (25.9% *vs* 3.2%). Moreover, Kim *et al*[96] presented significantly diverse recurrence rates in the patients without any prior manipulation (7.7%), with previous biopsy sampling (40.7%), and with advanced manipulation (53.8%) identifying previous resection attempts as a significant risk factor compared with non-manipulated lesions (OR = 18.8; $P = 0.001$). Besides, Nanda *et al*[97] showed for the lesions located in technically complicated sites such as ileum with/without valve involvement, an early and a late recurrence in 17.5% and 4.5% of patients, respectively.

Fortunately, most of such events are not an overwhelming barrier because they can be managed with further endoscopic therapy[107,112-115] when it is carried out with a regular surveillance program (3-6 mo) following the index endoscopy[3,5,32]. These relapses have been removed even with a 93% success rate for advanced colonic

adenomas up to 120 mm in size after conventional or wide-field EMR[10,17].

Thermal ablation/APC of margins at the resection site can be either an adjuvant treatment to clean suspicious margins to reduce recurrences or a subsequent therapeutic aid to eliminate the visible residual unresected after index EMR[21,23,114,115].

Renewed endoscopic treatment of recurrences is correlated with high curative rates, low complication rates, and a low risk of malignant evolution[111,112,115].

Brooker *et al*[112] showed a decrease of 50% of early relapse of large colorectal sessile polyps after combining EMR treatment with APC. The study by Kim *et al*[111] analyzing 70 recurrent lesions after the previous p-EMR of large non-pedunculated adenomas reported that 1 patient underwent surgery for an adenoma involving the ileocecal valve and another one underwent curative surgery for a deep SMIC. The rest of the patients were successfully managed endoscopically.

Furthermore, a recent large Australian randomized multicenter study (390 patients) of tertiary centers[115] confirmed reduced adenoma recurrence rates at early follow-up in patients treated with thermal ablation of the resection margins after the EMR of large LSTs as compared to controls without additional treatment (5.2% *vs* 21.0%, respectively). Otherwise, a small cohort Polish study[114] reported similar recurrence rates for large sessile polyps treated with both p-EMR and APC than those treated with only p-EMR (14% for both groups).

ESD: Indications, efficacy, safety, and recurrences

The endoscopic eradication of colorectal preneoplastic and neoplastic lesions has continuously changed and evolved in the last decades to develop ESD[116-119], a more challenging technique[5,21,26,91,120]. The ESD method was initially developed in Japan in the early 2000s for the resection of superficial carcinomas of the upper digestive tract[121-124], whereas Western areas used ESD especially for treating colorectal lesions[4,5,21,26,91]. However, the technical difficulty, the necessity for a lengthy training of the medical/nursing team, and the higher complication rate than conventional EMR have hampered widespread adoption in Western countries[1,2,5,21].

ESD can have both a diagnostic and therapeutic intent, although due to higher rates of perforation the diagnostic intent in the colon is limited[1,2,5,21]. This procedure aims at the *en bloc* and deep removal of large non-pedunculated lesions with a high potential of malignancy. These lesions need an accurate histological assessment for the risk of lymph node metastases, and *en bloc* R0 is mandatory in these cases with high suspicion of superficial submucosal invasion[5,21,22,52].

ESD uses dedicated needles that by cutting the mucosa and submucosa can enable an almost surgical resection of lesions > 20 mm that are otherwise not radically removable or only in several fragments, providing a lower recurrence rate of the lesions[1,2,5,21].

The Japan Gastroenterological Endoscopy Society[21], European Society of Gastrointestinal Endoscopy[2], and American Society for Gastrointestinal Endoscopy [5] guidelines were endorsed to provide specific recommendations on the appropriate use of ESD. These guidelines strongly advise ESD instead of EMR in the following cases[1,2,5,21,106]: for the removal of large sessile or non-polypoid tumors (including LST G and nodular mixed types) assumed to have superficial SMIC, carcinoma with shallow T1 SMIC, depressed or irregular type tumors, LSTs (pseudo-depressed) with an NG surface pattern, Kudo Vi-type PP, when regardless of the size a lesion is radically unremovable with snare EMR, tumors with submucosal fibrosis, local residual or recurrent early carcinomas after inefficacious endoscopic resection, or non-polypoid dysplasia/sporadic tumors in patients with inflammatory bowel disease.

Some studies have documented the efficacy and safety of ESD for treating sessile or non-polypoid lesions of any size, especially in Asian countries[5,123,125].

However, ESD has been complicated by late bleeding in 2%[123], 5%[125], 5.1%, and 13%[127] and by perforation in 2.5%[123], 3.2%[126], 4%[125], 7%[125], and 18%[127] of the procedures. Recurrence occurred in 4%[125], 7%[123], 7.5%[126], and 13.8%[65] of cases.

Specifically, a systematic review by Repici *et al*[128] evaluated, among 22 studies (91% Asian), the outcomes of 2841 sessile lesions or LSTs of any diameter [median of mean size, 32.4 mm (range 6.2-43.6 mm)] following ESD treatment. The *en bloc* and R0 rates were 91.6% and 88%, respectively, and significantly higher for Asians than Europeans (88% *vs* 65%, respectively) with a good safety profile (4% and 2% of the procedures were complicated by perforation or late bleeding, respectively). Furthermore, ESD showed a relapse rate of < 0.1%, whereas the estimation of surgery for complications was 1%[128].

A retrospective Japanese study[123] analyzed 1017 ESD procedures performed for sessile or non-polypoid lesions (mean size, 38 mm). *En bloc* resection was successful in 90% while R0 in 77% of cases[123]. Perforation and delayed bleeding rates were 2.5% and 2.0%, respectively. Relapses occurred in 7.5%[123]. A small prospective study[127] evaluating ESD outcomes in a French cohort of 45 patients (treated for sessile rectal tumors or LSTs ≥ 10 mm) showed fair *en bloc* resection rates (64%) as well as low curative R0 (53%). The complication rate was high (18% for perforation and 13% for late bleeding), while 7% relapsed during surveillance[127].

Another Japanese study[126] suggested the safety of ESD for treating early CRC; among the 373 analyzed patients, 82.4% had non-polypoid lesions and 17.3% sessile lesions (sized 28.6 ± 14.2 mm). Post-procedural perforation and bleeding rates occurred in 3.2% and 5.1% of cases, respectively.

A retrospective Japanese study[93] compared EMR and ESD techniques for treating 189 large tumors (including LST-G/LST-NG, and depressed/protruded lesions). Despite the ESD group had significantly larger tumor sizes (31.6 ± 9.0 vs 25.5 ± 6.8 mm, $P < 0.001$), longer procedural times (87.2 ± 49.7 vs 29.4 ± 26.1 min, $P < 0.001$), and higher perforation cases (5.9% vs 0%, $P = 0.04$), there occurred higher *en bloc* resection rates (83.5% vs 48.1%, $P < 0.001$) and fewer recurrences (1.2% vs 15.4%, $P = 0.002$) than EMR. Postoperative bleedings were similar in the two groups (2.4% vs 2.9%, $P =$ not significant)[93].

A systematic review[125] of 15 European studies determined the efficacy and safety of ESD for treating 1404 cases with large and complex lesions [mean size, 40 mm (range 24-59 mm)]. The *en bloc* resection rate was 83%, and the R0 rate was 70%[125]. Perforation and bleeding rates were 7% and 5%, respectively. The recurrence rate was 4% in a year of surveillance time[125].

Notably, in the presence of residual or locally recurrent lesions after previous EMR, a new variant of the ESD technique using double clip and rubber band traction has shown promising results, either for removing LSTs deeply invading appendiceal orifice[129-131] or recurrent sessile serrated adenomas invading the site of previous appendectomy[132,133]. Indeed, in a retrospective French study[129], ESD with double clip and rubber band traction of 53 residual/locally recurrent colonic lesions achieved *en bloc* and R0 resections in 92.5% and 79.2%, respectively. Intraoperative perforations and late bleeding occurred in 7.5% and 1.9%, respectively, although they were endoscopically managed. No complications requiring surgery occurred[129].

Nevertheless, following the limited ESD indications[1,2,5,21] and the greater attention on the indiscriminate use of this procedure are the results of the systematic review by Fuccio *et al*[22] published in 2018 of mixed Asian and European (51 included) studies[22]. Of the 11260 lesions treated with ESD, 82.2% were adenomas with low or high-grade dysplasia. Submucosal cancers were in 15.7% of cases, but only 8% had superficial SMIC. This percentage was reduced to 6% when the analysis was limited to oncologically curative events, with no statistically significant difference between the European and Asian studies. Therefore, most lesions could have been radically resected, even with p-EMR. This study considered even the clinical outcomes of standard ESD performed on 18764 lesions (of 97 studies). The rates of *en bloc* resection and R0 were 91% and 82%, respectively, with a 2% recurrence rate[22]. European studies, as compared to Asian ones, displayed lower R0 rates (71.3% vs 86.6%) and a higher incidence of adverse events. Late bleeding and perforation occurred in 4.2%/8.6% vs 2.4%/4.5%, respectively, thus confirming greater expertise of Eastern endoscopist[116].

Therefore, the unsolved question concerns the necessity of a reliable SMIC assessment system, able to stratify the risk of the post-procedural need for surgery after ESD. In other words, it should be capable of selecting the at-risk subgroups of patients in whom ESD could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy based on the morphologic features of colorectal non-pedunculated lesions according to current endoscopic technology, to wisely choose among EMR and ESD procedures.

Inclusion criteria

We included studies that assessed the morphological and imaging patterns predictive of SMIC of non-pedunculated colorectal lesions of any size before choosing among EMR or ESD procedures. We also included those studies comparing the two strategies, regardless of the techniques or devices employed.

Exclusion criteria

We excluded studies including colorectal lesions removed in patients with inflammatory bowel disease and those using surgery as a control group.

EMR vs ESD: Systematic reviews and meta-analyses

En bloc and R0: As shown in Table 2, a systematic review and meta-analysis[134], including four retrospective studies and 243 Asiatic patients, reported a significantly higher percentage of *en bloc* resection for sessile polyps (rectal carcinoids < 15 mm) in ESD than EMR group (100% *vs* 92%, respectively) and also a higher R0 of 87.7% than 69.1% (OR = 0.29; 95%CI: 0.14–0.58; *P* < 0.001), respectively.

A meta-analysis of six case-control studies[135] of Asian populations, including 893 patients treated for sessile or flat lesions ≥ 10 mm, reported a higher *en bloc* resection rate in the ESD group than the EMR group (87.9% *vs* 44.5%, respectively; OR = 7.94; 95%CI: 3.96–15.91; *P* < 0.001). Also, the ESD and EMR groups did not significantly differ in terms of R0 resection rates [83.8% *vs* 65.5 %, respectively; OR = 1.65; 95%CI: 0.29–9.30; *P* = not significant].

A systematic review and meta-analysis of four retrospective studies[136] enrolled 216 patients of Asian populations endoscopically treated for rectal carcinoids of size ≥ 10 mm. A non-significant difference of *en bloc* resection (90.6% *vs* 93.6%; OR = 0.82; 95%CI: 0.25–2.70; *P* = 0.74) and R0 (79.4% and 78%; OR = 1.53; 95%CI: 0.62–3.73; *P* = 0.35) between ESD and EMR methods was shown.

Another meta-analysis of seventeen heterogeneous retrospective Chinese studies [137], evaluating the endoscopic outcomes of 2003 sessile polyps (≥ 5 mm) (mostly carcinoids), revealed a significantly higher *en bloc* resection rate (92.0% *vs* 89.8%, respectively; OR = 2.81; 95%CI: 1.39–5.70; *P* = 0.004) using ESD than EMR as well as higher R0 rates (86.5% *vs* 61.4%, respectively; OR = 2.81; 95%CI: 1.39–5.70; *P* < 0.004) for the ESD group.

Moreover, a meta-analysis of eight Japanese studies[103], including six cohort studies and two case-control series for a total of 1262 patients, compared endoscopic resection of sessile lesions of variable size and confirmed the highest percentages of *en bloc* resection (91.7% *vs* 46.7%; OR = 6.84; 95%CI: 3.30–14.18; *P* < 0.001) and R0 resection (80.3% *vs* 42.3%; OR = 4.26; 95%CI: 3.77–6.57) using ESD than EMR.

A systematic review with meta-analysis[138] related to eleven retrospective studies (eight of them evaluating sessile polyps and three of any LST ≥ 20 mm) including 4678 Asian and French patients, displayed higher rates of *en bloc* resection (89.9% *vs* 34.9%; OR = 1.93; 95%CI: 1.46–2.54; *P* < 0.001) and R0 resection (79.6% *vs* 36.2%; OR = 2.01; 95%CI: 1.76–2.29; *P* < 0.001) for ESD than EMR.

Finally, in a systematic review of 66 Western and Asian studies[107] evaluating a total of 13659 sessile polyps/LST lesions, the percentage of *en bloc* resection was 90.5% after ESD and 62.8% following EMR (OR = 0.18; 95%CI: 0.16–0.2; *P* < 0.001). Notably, the R0 curative rate was higher after EMR (92.0% *vs* 82.1%; OR = 2.5; 95%CI: 2.2–2.7; *P* < 0.001).

Tumor size: The tumor size was larger in the ESD group as compared to EMR in the three meta-analyses of Chao *et al*[137] (mean size not specified, OR = 3.09; 95%CI: 1.54–4.63; *P* < 0.001), Fujiya *et al*[103] (mean size was reported only for three studies, OR = 7.38; 95%CI: 6.42–8.34), and Arezzo *et al*[138] (33.7 mm *vs* 27.4 mm, OR = 7.36; 95%CI: 6.27–8.45; *P* < 0.001). The size of lesions in the other three studies was similar for all groups[134–136].

Adverse events: The perforation rate was higher in the ESD group, whereas the delayed bleeding rate was similar to the EMR group in the four studies of Chao *et al* [137] (5.9% *vs* 1.5%; OR = 5.27; 95%CI: 2.75–10.08; *P* < 0.001 and 3.7% *vs* 3.3%; OR = 1.34; 95%CI: 0.81–2.20; *P* = 0.25), Fujiya *et al*[103] (8.5% *vs* 0%; OR = 4.96; 95%CI: 2.79–8.85 and 2.0% *vs* 3.5%; OR = 0.85; 95%CI: 0.45–1.60), Arezzo *et al*[138] (4.9% *vs* 0.9%; OR = 3.19; 95%CI: 2.14–4.77; *P* < 0.001 and 1.9% *vs* 2.9%; OR = 0.68; 95%CI: 0.44–1.03; *P* = 0.070), and De Ceglie *et al*[107] (4.8% *vs* 0.9%; OR = 0.19; 95%CI: 0.15–0.24; *P* < 0.001 and 2.04% *vs* 2.27%; OR = 1.1; 95%CI: 0.9–1.4; *P* = 0.3), respectively.

Moreover in the study of De Ceglie *et al*[107], there was no meaningful difference in bleeding risk for ESD and EMR procedures. Also, ESD showed similar rates of post-procedural bleeding (3.6% *vs* 8.0%) and perforation (0.7% *vs* 8.0%) than the EMR group according to Zhong *et al*[134] and similar overall complication rates as observed by Wang *et al*[136] (18.3% *vs* 10.3%; OR = 0.67; 95%CI: 0.26–1.69; *P* = 0.40) and by Wang *et al*[135] (8.9% *vs* 5.8%).

Recurrence: ESD was associated with a lower recurrence rate than EMR in the six studies of Wang *et al*[135] (0.98% *vs* 12.70%; OR = 0.09; 95%CI: 0.04–0.19), Wang *et al* [136] (0.9% *vs* 6.4%; OR = 0.15; 95%CI: 0.03–0.87; *P* = 0.03, when using the fixed-effect model), Chao *et al*[137] (1.0% *vs* 9.9%; OR = 0.14; 95%CI: 0.06–0.30; *P* < 0.001), Fujiya *et al*[103] (0.9% *vs* 12.2%; OR = 0.08; 95%CI: 0.04–0.17), Arezzo *et al*[138] (0.7% *vs* 12.7%;

Table 2 Characteristics of the seven included systematic reviews and meta-analyses on the comparison between the outcomes for endoscopic mucosal resection and endoscopic submucosal dissection procedures

Ref.	Study	Nations	N patients/lesions	Type of colorectal lesions	Lesion size	Procedural time ¹	En bloc resection ¹	R0 ¹	Perforation ¹	Bleeding ¹	Surgery ¹	Recurrence ¹
Zhong <i>et al</i> [134], 2013	Systematic review with meta-analysis of 4 retrospective studies	Japan, Korea, China	243 patients/245 lesions (EMR: 106; ESD: 139)	Sessile (carcinoids)	< 15 mm	19.1 ± 11.1 vs 8.1 ± 9.4	92% vs 100%	69.1% vs 87.7%	2.8% vs 0.7%	2.8% vs 3.6%	0.7% vs 0%	2.9% vs 0%
Wang <i>et al</i> [135], 2014	Meta-analysis of 6 studies (case-control)	Japan, Korea	893 patients/1642 lesions (EMR: 866; ESD: 776)	Sessile or flat	≥ 10 mm	Range, 29.0-29.4 vs 87.2-108.0 min	44.5% vs 87.9%	65.5% vs 83.8%	5.8% vs 8.9% (overall complications)		NA	12.70% vs 0.98%
Wang <i>et al</i> [136], 2016	Systematic review with meta-analysis of 4 retrospective studies	Brazil, Korea, Japan, China	216 patients/216 lesions (EMR: 109; ESD: 107)	Rectal carcinoids (lesion morphology not specified)	≥ 10 mm	(150.0 ± 66.3/116.0 ± 58.5 ± 3.6/63.0 ± 54.0/50.0 ± 589.2) vs (133.0 ± 94.8/84.0 ± 51.2/131.0 ± 100.0/78 ± 176.7) min	93.6% vs 90.6%	78% vs 79.4%	10.3% vs 18.3% (overall complications)		NA	6.4% vs 0.9%
Chao <i>et al</i> [137], 2016	Meta-analysis of 17 studies (retrospective)	China	2003 patients/2003 lesions (EMR: 1054; ESD: 949)	Sessile: carcinoids (11 studies) or carcinomas (5 studies); LST (1 study)	≥ 5 mm	Range, 15.0-65.9 vs 3.5-29.4 min	89.8% vs 92.0%	61.4% vs 86.5%	1.5% vs 5.9%	3.3% vs 3.7%	NA	9.9% vs 1.0%
Fujiya <i>et al</i> [103], 2015	Meta-analysis of 8 studies (non-randomized, 6 cohort and 2 case-control)	Japan	1262 patients (EMR: 634; ESD: 628)/1763 lesions (EMR: 949; ESD: 814)	Morphological features of lesions in 7 studies were ² , in the EMR group: 0-I (269 cases) and 0-II (679 cases); in the ESD group: 0-I (125 cases) and 0-II (680 cases); 576 adenomas and 380 carcinomas	≥ 20 mm (5 studies), ≥ 10 mm (1 study), > 5 mm (1 study)	Range, 29.0-30.0 vs 65.9-108.0 min	46.7% vs 91.7%	42.3% vs 80.3%	0% vs 8.5%	3.5% vs 2.0%	5.8% vs 9.9%	12.2% vs 0.9%
Arezzo <i>et al</i> [138], 2016	Systematic review with	Japan, Korea, France	4678 patients/4678	Sessile (LST-NG and LST-G	≥ 20 mm (except in 3	29.1 vs 66.5 min	34.9% vs 89.9%	36.2% vs 79.6%	0.9% vs 4.9%	2.9% vs 1.9%	3.0% vs 7.8%	12.7% vs 0.7%

	meta-analysis of 11 studies (10 retrospective and 1 case-control)		lesions (EMR: 3161; ESD: 1517)	were also included in 3 studies): adenomas, carcinomas in situ, invasive cancers or carcinoids	studies)								
De Ceglie <i>et al</i> [107], 2016	Systematic review of 66 studies (3 RCTs; 22 prospective and 41 retrospective)	Germany, Taiwan, France, Japan, Greece, Great Britain, Czech Republic, Malaysia, Australia, Italy, China, United States, Brazil, Korea, Portugal, Serbia	13659 patients (EMR: 8660; ESD: 4999)/17950 lesions (EMR: 11.873; ESD: 6077)	Sessile or LST	LST-NG ≥ 20 mm and for LST-G ≥ 30 mm or ≥ 40 mm	NA	62.8% <i>vs</i> 90.5%	92.0% <i>vs</i> 82.1%	0.9% <i>vs</i> 4.8%		2.3% <i>vs</i> 2.0%	NA	10.4% (3.0% in <i>en bloc</i> and 12% in piecemeal) <i>vs</i> 1.2%

¹Endoscopic mucosal resection *vs* Endoscopic submucosal dissection.

²According to Paris classification. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST: Laterally spreading tumor; NG: Non-granular type; G: Granular type; RCT: Randomized controlled trial; NA: Not available.

OR = 0.06; 95%CI: 0.03–0.11; $P < 0.001$), and De Ceglie *et al* [107] (1.2% *vs* 10.4%; OR = 8.19; 95%CI: 6.2–10.9; $P < 0.001$). Only one meta-analysis [134] showed a similar recurrence rate between ESD and EMR (0% *vs* 9%).

Surgery rates: The data for the surgical rate for any reason was available only in three studies [103,134,138].

In the meta-analysis of Zhong *et al* [134], one patient underwent surgery as rescue therapy for non-manageable recurrence after EMR and none in the ESD group (0.7% *vs* 0%, $P =$ not significant).

In the meta-analysis of Fujiya *et al* [103], the most frequent indication for additional surgery was, for both ESD and EMR groups, non-curative reasons rather than perforation (9.9% *vs* 5.8%; OR = 2.16; 95%CI: 1.16–4.03; $P < 0.001$). This resulted from the analysis of two studies.

In the study by Arezzo *et al* [138], the overall surgery requirement for complications was higher in the ESD group (7.8% *vs* 3.0%; OR = 2.40; 95%CI: 1.51–3.82; $P < 0.001$). In detail, the rates of surgery for complications (OR = 7.21; 95%CI: 2.19–23.76; $P < 0.001$), and surgery for non-curative reasons (OR = 1.55; 95%CI: 1.03–2.33; $P < 0.034$) were 3.0% and 6.9%, respectively, in the ESD group and 0.4% and 4.1% in the EMR group.

CONCLUSION

Conclusively, it is crucial to enhance the preoperative diagnostic workup because the prevailing technology concomitantly with operator skills is still exceedingly misleading, especially in deciding the most suitable endoscopic method for radical resection of non-pedunculated colorectal lesions at risk of underlying malignancy. Admittedly, the prevailing unsolved challenge concerns the requirement for a secure SMIC estimation method to properly stratify the chance of the post-procedural necessity for surgery following ESD and proficient in determining the at-risk subgroups of patients in whom ESD could obtain the most fitting approach.

Additionally, ESD necessitates being further improved considering the excessively time-consuming as well as the intraprocedural technical hindrances and related complications, even in expert hands.

Therefore, in this time frame, it is demanded a substantial ability to choose and perform EMR when it is proper and ESD only when obliged by the highly suspected endoscopic features of colorectal lesions.

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Endo-hepatology: An emerging field

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Author contributions: Hogan DE and Ma M wrote the paper; Kadosh D, Menon A, Chin K collected articles for review; Swaminath A oversaw the entire process.

Conflict-of-interest statement: The authors of this review have no significant conflicts of interest to disclose.

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology

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Abstract

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver disease has traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined. Here we discuss several EUS-guided procedures such as liver biopsy, shear wave elastography, direct portal pressure measurement, paracentesis, as well as EUS-guided therapies for variceal hemorrhage.

Key Words: Endoscopic ultrasound; Therapeutic endoscopic ultrasound; Hepatology; Liver disease; Liver biopsy

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Core Tip: Endo-hepatology in an emerging field which utilizes diagnostic and therapeutic endoscopic ultrasound to help gastroenterologists diagnose and manage liver disease. Our paper will focus on liver biopsy, ultrasound and shear wave elastography, ascitic fluid sampling, portal pressure measurement, management of varices, and vascular interventions.

Citation: Hogan DE, Ma M, Kadosh D, Menon A, Chin K, Swaminath A. Endo-hepatology: An emerging field. *World J Gastrointest Endosc* 2021; 13(8): 296-301

and hepatology

Country/Territory of origin: United States**Peer-review report's scientific quality classification**

Grade A (Excellent): A
 Grade B (Very good): 0
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: March 16, 2021**Peer-review started:** March 16, 2021**First decision:** May 4, 2021**Revised:** June 13, 2021**Accepted:** July 16, 2021**Article in press:** July 16, 2021**Published online:** August 16, 2021**P-Reviewer:** Karagoyozov PI**S-Editor:** Zhang H**L-Editor:** A**P-Editor:** Wang LYT**URL:** <https://www.wjgnet.com/1948-5190/full/v13/i8/296.htm>**DOI:** <https://dx.doi.org/10.4253/wjge.v13.i8.296>

INTRODUCTION

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver disease has traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined endo-hepatology which puts new endoscopic tools in the gastroenterologist hands[1,2]. Liver disease in pre-cirrhotic and cirrhotic populations present different challenges. Pre-cirrhotic disease requires longitudinal management to evaluate fibrosis severity and strategies to prevent progression, whereas cirrhotic liver disease presents challenges in the management of portal hypertension. Additionally, biliary and hepatic malignancy can present challenges to diagnosis and therapy that may be obviated by new techniques. Our paper will describe the role of endo-hepatology in these increasingly prevalent conditions.

LIVER BIOPSY

Liver biopsy has long been considered the gold standard to differentiate between several types of liver disease, using histological findings to distinguish between autoimmune etiologies, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, *etc.* Traditional liver biopsy involves a 16 or 18 gauge needle and a percutaneous approach. These biopsies were at one point targeted using a percussion method, however, this has been largely replaced by ultrasound (US) or computed tomography (CT) guided methods[3]. Despite imaging guidance, percutaneous liver biopsy can still lead to complications such as pain, hemorrhage, tumor-seeding, intestinal perforation, peritonitis, hemothorax or pneumothorax, bacteremia, and even death. Transjugular liver biopsy emerged as a safer alternative, particularly in patients with massive ascites, obesity, or coagulopathy[4], though this approach still carries a relatively high complication rate near 7%, including pseudoaneurysm, hemorrhage, bile leak, pneumothorax, and ventricular arrhythmia[5]. Through esophageal, gastric, and duodenal views, EUS offers exceptional detail in evaluating the biliary tract, liver, pancreas, stomach, esophagus, and mediastinal structures. Unlike conventional US or CT, EUS allows the liver to be visualized or conceptualized in a three-dimensional view, allowing the liver to be viewed through the Couinaud classification which divides the liver into eight separate functional units. Due to proximity, direct echoendoscopic visualization, and utilization of doppler ultrasound, there is increased potential for diagnostic success and a low rate of adverse events (estimated approximately 2.5%)[6] with EUS-guided liver biopsy[7]. The technique involves a linear echoendoscope which can locate either the right or left hepatic lobe. Using a fine needle biopsy (FNB) needle with a vacuum syringe, the endoscopist has the ability to biopsy either or both lobes of the liver, and allows for several actuations with a single puncture of the liver capsule[8]. This approach can also offer a simultaneous endoscopic esophageal variceal screening, or endoscopic shear wave elastography (SWE) or portal pressure gradient (PPG) measurement[9].

NON-INVASIVE MEASUREMENT OF FIBROSIS

Imaging such as SWE has proven useful as a non-invasive tool for measuring liver fibrosis with a correlation to histologically measured liver fibrosis[10]. This correlation, though, is affected by variability between the right and left lobe of the liver as transcutaneous SWE is typically performed over the right lobe of the liver[11]. Newer EUS processors have the capability to carry out SWE both in the right and left lobe of the liver, allowing for the assessment of fibrosis during endoscopy. While more invasive than traditional transcutaneous SWE, in those already undergoing endoscopic evaluation or those with a body mass index > 35 which may require a special probe to

assure accuracy, EUS-SWE appears to be both feasible and reliable[9,12]. Two-dimensional ultrasound views during EUS-SWE or EUS alone can also allow for routine hepatocellular carcinoma screening. Doing so during an EUS allows for simultaneous FNB of small or suspicious lesions which may be found during EUS evaluation[8,13].

PORTAL PRESSURE MEASUREMENT

Portal hypertension is the driving force for complications in liver fibrosis and cirrhosis. Portal venous pressure (PVP) measurement, therefore, is a key to anticipating complications. The current technique is similar to transjugular liver biopsy, during which a catheter is inserted into the jugular vein and advanced into the hepatic vein. The portal vein is not directly accessible *via* this approach, but the pressure can be estimated using wedge hepatic venous pressure (WHVP). The intravascular catheter is able to directly measure the WHVP and the free hepatic venous pressure, the difference of which is the PPG, which reflects the degree of portal hypertension (PH) and PVP[14]. In 2004, a porcine model was used to demonstrate the ability to use EUS to directly access the portal vein and measure portal venous pressure (PVP). This has been recreated in humans in a pilot study using a linear echoendoscope, a 25 gauge access needle, and a compact manometer. The portal vein and hepatic vein are able to be accessed directly, and their pressures measured *via* the manometer. PVP was able to be measured and had a high degree of correlation with clinical and endoscopic parameters of PH including thrombocytopenia, ascites, portal hypertensive gastropathy, and gastroesophageal varices[14]. Despite the significant correlation of PVP to clinical outcomes, PPG remains as the current standard for measurement and is estimated *via* the WHVP rather than direct measurement of portal vein. With additional expertise and safety outcomes data, one may yet find a role for this technology and technique in patient's where traditional techniques will be ineffective, such as those with hepatic vein clots or those who have undergone prior vascular interventions.

COMPLICATIONS OF PORTAL HYPERTENSION: ASCITES

Ascites is another common manifestation of advanced liver disease, often thought to be from an imbalance in the resorption of fluid due to elevated portal and oncotic pressure. The etiology of ascites and evidence of spontaneous bacterial peritonitis requires sampling the fluid directly. This is frequently done with a combination of imaging and abdominal paracentesis. EUS offers another modality to access ascitic fluid with higher sensitivity than CT and transabdominal ultrasound[15,16]. The ability of EUS to sample retroperitoneal and intra-abdominal collections and masses can also be applied to ascitic fluid. EUS has been previously described for use in direct sampling of fluid collections that may not be amenable to percutaneous drainage due to small volume or loculated collections[17]. EUS-guided paracentesis (EUS-P) has been shown to be technically feasible, however, the significance of risk associated with EUS-P including infection, contamination, and seeding of malignancy remains unknown. This is highlighted by the limitation that EUS-P cannot be performed in a sterile fashion as it requires puncture through the bowel lumen[18].

COMPLICATIONS OF PORTAL HYPERTENSION: VARICES AND VARICEAL HEMORRHAGE

The initial management of both bleeding and non-bleeding esophageal and gastric varices has largely been endoscopic[19]. All cirrhotic patients should undergo screening for esophageal varices after their diagnosis. The grading of varices can be quite subjective and is endoscopist dependent, taking into account diameter, location, character, and tortuosity of the vessel. In several studies, EUS has been more effective than esophagogastroduodenoscopy (EGD) in the detection of gastric and paraesophageal varices. Many of these lesions can appear as folds or submucosal lesions, but EUS allows the endoscopist to view below the mucosal surface and utilize doppler to evaluate for blood flow. The use of doppler ultrasound increases the ability to detect varices, particularly in the duodenum, and collateral vasculature. Some EUS findings

can also be used to determine the risk of variceal hemorrhage by evaluating the cumulative cross-sectional area of all distal esophageal varices, with a 76-fold increase per year with each 1 cm² increase in cumulative area. The utility of EUS in minimizing interobserver variability is limited by correlation with EGD and the lack of a standardized grading system for varices seen during EUS. Kane *et al*[20] applied transnasal high-resolution endoluminal ultrasound (HRES) and was able to demonstrate correlation to EGD. Furthermore, application of transnasal HRES allows examination without sedation.

Injection sclerotherapy, variceal ligation (EVL), or cyanoacrylate glue injection is usually performed relatively blindly during treatment of acute hemorrhage. EUS can allow for visualization of the lumen of the varix[21]. EVL has been the treatment of choice for esophageal variceal hemorrhage and for secondary prevention. Usually several endoscopies are required for complete variceal containment, and the most common post-procedure complication is post-EVL induced bleeding with an incidence of roughly 2.8%. This can be treated with a course of proton pump inhibitors, and further endoscopic interventions such as sclerotherapy or transjugular intrahepatic portosystemic shunt (TIPS) placement[22].

Injection of cyanoacrylate glue has been shown to have improved hemostasis and lower rebleeding rates in the treatment of gastric varices when compared to EVL[23]. This method, however, is technically more challenging and complications can be severe, including pulmonary and cerebral emboli. EUS-guided cyanoacrylate injection allows for direct visualization of the culprit vessel and confirmation of hemostasis utilizing doppler ultrasound[24]. EUS-guided microcoil embolization has been evaluated as a method of hemostasis with comparable efficacy and a decreased risk of migration or distant emboli[25]. Recently, EUS-guided deployment of coils in conjunction with cyanoacrylate injection has been demonstrated to reduce the risk of glue embolization, and can be more effective than coil embolization alone[26].

When endoscopic therapy of variceal hemorrhage is unsuccessful, interventional vascular procedures such as TIPS or balloon-occluded retrograde transvenous obliteration have been employed[22]. Recent studies using a porcine model have shown that even these predominantly surgical or endovascular procedures can also theoretically be carried out using EUS. Using an access needle, the hepatic vein is accessed, and a catheter is advanced further into an accessible branch of the portal vein. Using a lumen-apposing metal stent, the hepatic vein and portal vein are fistulized[27]. While this study was small and simply a proof-of-concept, it illustrates the future applications of EUS in the world of hepatology.

CONCLUSION

EUS-guided interventions may appear more invasive than the traditional percutaneous or intravascular procedures. However, when advantages in recovery time, diagnostic yield, and complication rates are factored in, the EUS-guided procedures may be more efficient, thus more cost-effective. This is particularly apparent considering multiple interventions can be combined into a single endoscopic procedure[8,9]. Furthermore, endoscopic screening and surveillance are commonly implemented in management of advanced liver disease, decreasing the overall risk applied by addition of EUS evaluation. More data regarding feasibility and safety is needed-particularly in regards to EUS-guided paracentesis, portal pressure measurement, and portosystemic shunting-and while endo-hepatology remains in its infancy, interventional EUS is well on its way to becoming an integral part of routine liver disease management and care.

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Endoscopic ultrasound-guided biliary drainage: Are we there yet?

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Conflict-of-interest statement: None of the authors have any conflict of interests.

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Manuscript source: Invited manuscript

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is the mainstay procedure of choice for management of obstructive biliary disease. While ERCP is widely performed with high success rates, the procedure is not feasible in every patient such as cases of non-accessible papilla. In the setting of unsuccessful ERCP, endoscopic ultrasound-guided biliary drainage (EUS-BD) has become a promising alternative to surgical bypass and percutaneous biliary drainage (PTBD). A variety of different forms of EUS-BD have been described, allowing for both intrahepatic and extrahepatic approaches. Recent studies have reported high success rates utilizing EUS-BD for both transpapillary and transluminal drainage, with fewer adverse events when compared to PTBD. Advancements in novel technologies designed specifically for EUS-BD have led to increased success rates as well as improved safety profile for the procedure. The techniques of EUS-BD are yet to be fully standardized and are currently performed by highly trained advanced endoscopists. The aim of our review is to highlight the different EUS-guided interventions for achieving biliary drainage and to both assess the progress that has been made in the field as well as consider what the future may hold.

Key Words: Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided rendezvous; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-guided gallbladder drainage; Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography

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Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): D
Grade E (Poor): 0

Received: March 17, 2021

Peer-review started: March 17, 2021

First decision: May 4, 2021

Revised: May 14, 2021

Accepted: July 14, 2021

Article in press: July 14, 2021

Published online: August 16, 2021

P-Reviewer: Aparicio JR, Kuraoka N, Miyabe K, Scimeca D, Siripun A

S-Editor: Fan JR

L-Editor: A

P-Editor: Xing YX



Core Tip: Endoscopic ultrasound-guided biliary drainage (EUS-BD) has emerged as a promising procedure for the management of obstructive biliary disease following failed endoscopic retrograde cholangiography. A number of different techniques have been described, with both intrahepatic and extrahepatic approaches. Using EUS-BD, either transpapillary or transluminal biliary decompression can be attained. Increased experience in these techniques along with introduction of novel devices and stents has led to improved outcomes when performing EUS-BD.

Citation: Pawa R, Pleasant T, Tom C, Pawa S. Endoscopic ultrasound-guided biliary drainage: Are we there yet? *World J Gastrointest Endosc* 2021; 13(8): 302-318

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/302.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.302>

INTRODUCTION

For decades, endoscopic retrograde cholangiopancreatography (ERCP) has remained the gold standard procedure for management of biliary obstruction. The success rate of this procedure in achieving deep cannulation of the desired duct ranges from 89%-92% using conventional techniques[1-3]. Advanced techniques to achieve biliary or pancreatic access have shown to improve cannulation up to 97%[4]. Common causes of ERCP failure include distortion of the ampulla secondary to malignant infiltration or periampullary diverticulum. In addition, non-accessible papilla secondary to surgically altered gastrointestinal (GI) anatomy or gastric outlet obstruction (GOO) secondary to benign or malignant diseases can also result in failure[5]. Conventionally, percutaneous transhepatic biliary drainage (PTBD) was the rescue therapy in the setting of ERCP failure. While PTBD has a high success rate, drainage complications including tube occlusion or dislodgement and cholangitis continue to be a major problem along with significantly reduced quality of life[6,7].

The use of endoscopic ultrasound (EUS) for performing cholangiopancreatography was first reported by Wiersema *et al*[8] in 1996. In 2001, Giovannini *et al*[9] first described the use of EUS for biliary drainage (EUS-BD)[9]. Since that time, a number of studies have compared EUS-BD to PTBD, finding similarly high rates of technical success, but lower rates of procedure-related complications as well as need for re-intervention with EUS-BD[10-12]. Recent meta-analyses and systematic reviews have offered the same conclusion, recommending EUS-BD over PTBD in the setting of ERCP failure due to higher rates of clinical success, fewer adverse events, and better quality of life[13,14].

The aim of this review is to describe recent advancements in EUS-BD with up-to-date techniques for achieving biliary access and drainage in patients with benign and malignant biliary obstruction where standard ERCP cannot be performed (Table 1).

EUS-GUIDED RENDEZVOUS

EUS-guided rendezvous (EUS-RV) as a salvage technique after unsuccessful ERCP was first described by Mallory *et al*[15] in 2004. This technique is used when the papilla is accessible, but deep cannulation cannot be achieved during ERCP. EUS-RV can be performed using a transhepatic or extrahepatic approach. For the transhepatic approach, the linear echoendoscope is placed in the stomach and a dilated segment II or segment III biliary branch is punctured with a 19-gauge needle. Following cholangiogram, a long (450 cm) 0.025 inch or 0.035 inch guidewire is advanced downstream into the duodenum. The extrahepatic approach involves puncture of the common bile duct (CBD) from the duodenal bulb (D1) or second portion of the duodenum (D2) followed by guidewire manipulation past the ampulla into the small bowel. Biliary cannulation is then re-attempted using a standard duodenoscope along the EUS-placed guidewire or the distal end of the guidewire is grasped with a forceps or snare and withdrawn *via* the accessory channel in the scope followed by a conventional ERCP[16].

Table 1 Endoscopic ultrasound-guided biliary drainage procedures

	EUS-BD procedures
1	EUS-guided rendezvous
2	EUS-guided choledochoduodenostomy
3	EUS-guided hepaticogastrostomy
4	EUS-guided gallbladder drainage
5	EUS-directed transgastric ERCP

EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; BD: Biliary drainage.

Different standardized algorithms have been proposed, often recommending initial approach from the D2 position if possible, followed by the D1 position and eventually transhepatic (*via* the stomach) if needed[16,17]. This recommendation is based on a number of factors including distance from puncture to ampulla and direction of needle position. A transhepatic approach requires a longer path to the papilla but requires less manipulation and steering of the guidewire compared to the extrahepatic approach. A study that compared extrahepatic *vs* transhepatic approach found similar success rates (100% *vs* 94.1%) in the two groups, but higher rates of post-procedure pain (5.5% *vs* 41.7%, $P = 0.017$), longer procedure times (25.7 min *vs* 34.4 min, $P = 0.0004$) and longer duration of hospitalization (2.52 d *vs* 0.17 d; $P = 0.0015$) in the transhepatic group[18].

One advantage of a transhepatic approach is the ability to perform EUS-guided antegrade therapy (EUS-AG) in patients following failed ERCP and inaccessible papilla. The technique can be performed in patients with surgically altered GI anatomy in which conventional EUS-RV is not feasible. Similar to the steps of EUS-RV, a guidewire is placed into the biliary system and advanced through the bile duct into the duodenum. This is followed by dilation of the fistulous tract if required. Subsequent biliary interventions such as stricture dilation, stone removal and transpapillary stent placement are then performed in an antegrade fashion without switching to a duodenoscope.

Iwashita *et al*[19] performed EUS-AG stenting in 20 patients with surgically altered GI anatomy who presented with malignant biliary obstructions (MBO)[19]. Technical and clinical success was achieved in 95% (19/20) of patients. The authors observed that approaching *via* the segment II intrahepatic allowed for a straighter approach course through the papilla. In a study using EUS-AG for management of biliary stones in patients with surgically altered GI anatomy, successful stone removal was performed in 72% (21/29) patients[20]. One major limitation of EUS-AG is the difficulty of reintervention if needed. In these cases, repeat EUS-AG or EUS-hepaticogastrostomy may need be performed.

Guidewire manipulation through the ampulla into the duodenum proves to be a difficult step in EUS-RV and is a common cause of failure. Angled tip guidewires have allowed endoscopists more maneuverability when adjusting trajectory in the biliary tree. Shearing of the guidewire has been documented as a potential complication following intense manipulation[21]. Martínez *et al*[22] reported good procedural success (80.6%) using a 22-gauge needle and 0.018 inch guidewire in cases with benign pathology and non-dilated ducts, where use of a 19-gauge needle often proves difficult [22]. More recently a steerable access system (Beacon EUS Access System; Covidien/Medtronic, Inc, Dublin, Ireland) has been designed allowing better control of the direction of wire through the biliary system. In a study by Ryou *et al*[23] using this steerable access device for EUS-BD, guidewire advancement in the intended direction was successful in 100% cases without any reported cases of wire shearing [23].

EUS-RV has been used as an alternative to precut papillotomy for achieving biliary access following ERCP failure. A retrospective study comparing precut papillotomy to EUS-RV showed higher success rate in achieving biliary access in the EUS-RV group (98.3 *vs* 90.3%, $P = 0.038$) with similar degree of adverse events in both groups (3.4% in EUS *vs* 6.9% in precut)[24]. In a later study, Lee *et al*[25] compared two groups of patients failing standard ERCP. Following failed cannulation, patients in group one underwent precut papillotomy and/or EUS-BD, while patients in group two only had precut papillotomy available. It was observed that group one patients had a significantly lower ERCP failure rate compared to group two patients (1% *vs* 3.6%).

Additionally, patients who underwent EUS-BD had higher success rates overall when compared with patients undergoing precut papillotomy alone (95.1% *vs* 75.3%)[25]. Despite these findings, precut papillotomy is often used as a first line salvage therapy in patients with failed biliary cannulation due to high success rate with experienced endoscopists, and lack of widespread availability of EUS expertise and equipment[26].

One of the limitations for EUS-RV is difficulty in advancing the guidewire through a malignant stricture and past the ampulla for performing ERCP. Given the lower success rates of EUS-RV compared to other forms of EUS-BD in malignant biliary disease, EUS-RV is preferred for managing patients with benign conditions such as choledocholithiasis and post-cholecystectomy bile leak[27].

EUS-GUIDED CHOLEDOCHODUODENOSTOMY

EUS-guided choledochoduodenostomy (EUS-CDS) is a transluminal technique that results in formation of a fistula connecting the duodenum and the dilated CBD[28]. It is commonly used in patients with distal MBO following failed cannulation.

This technique involves using a linear echoendoscope to identify the CBD from the duodenal bulb. The bile duct is then punctured using a 19-gauge needle and the needle position is confirmed by aspiration of bile and injection of contrast to perform a cholangiogram. A guidewire is then advanced through the needle towards the main biliary confluence, following which the needle is removed and the tract dilated (balloon dilators, cystotomes, needle knives, or graduated dilation catheters). Following dilation of the fistulous tract, a stent is placed across the choledochoduodenostomy site into the extrahepatic bile duct[29]. The first report on EUS-CDS was published in 2001 with placement of a 10 Fr plastic stent between the duodenum and CBD[9]. Further case reports described success with this technique, noting specific benefits including the ability to access the bile duct in a safe and stable manner, away from an obstructive tumor causing distal MBO[30,31].

Plastic stents (PS) were initially used for biliary drainage in EUS-CDS; however, high rates of complications were noted with these stents[32]. In a 2011 review on stent selection for EUS-BD, the authors observed shorter patency along with increased risk of bile leak, migration and dislocation with PS when compared with self-expanding metal stents (SEMS)[33]. Hara *et al*[34,35] conducted two clinical studies, one using PS and one fully covered (FC)-SEMS, for EUS-CDS and found a higher stent occlusion rate associated with PS (53% patients) compared to FC-SEMS (11% patients)[34,35]. Similar results were observed in a 2016 study by Khashab *et al*[36], where significantly more adverse events were seen in patients undergoing plastic stenting (42.86%) compared to patients treated with metal stents (13.08%)[36]. Uncovered SEMS (UC-SEMS) are generally avoided as the initial stent in EUS-CDS as there is not a formed tract between the bile duct and the intestine, leading to a risk of bile leak.

A prospective study of 34 patients with unresectable MBO who underwent EUS-CDS with covered metal stent reported high technical (97%) and functional success (100%)[37]. However non-tumor related recurrent biliary obstruction (RBO) was seen in 29% patients secondary to stent migration (18%), sludge/food impaction (9%) and duodenal wall impaction (3%). The median cumulative time to RBO was 11.3 mo (95% CI: 7.4-NA). Despite achieving high success rates of EUS-CDS with FC-SEMS, stent migration following placement was a worrisome complication, likely attributed to their large size, tubular shape and rigid properties[38-40]. At times, endoscopists chose to first place an UC-SEMS to decrease the likelihood of stent migration, followed by FC-SEMS placement into the existing stent to prevent bile leakage[33].

The high rate of complications observed with plastic and tubular metal stents led to the use of a novel, fully covered lumen-apposing self-expanding metal stent (LAMS) for EUS-CDS. This stent was originally designed for drainage of pancreatic fluid collections. The AXIOS LAMS (AXIOS, Boston Scientific, Marlborough, MA, United States) has bilateral flanged ends which provide anchorage across non-adherent luminal structures, thereby decreasing the risk of stent displacement, bile leak and preventing tissue ingrowth[41,42]. Further advancements were made with the introduction of the electrocautery (EC)-enhanced delivery system which merged puncture and release of the stent in a single step[43]. This system removes the need for separate needle puncture, tract dilation and multiple guidewire exchanges which in turn may reduce risk of complications as well as procedure duration. The delivery system also allows the endoscopist to release the bilateral flanges independent of one another, preventing premature deployment of the proximal flange. The stent is available in different diameters and lengths (6 mm × 8 mm, 8 mm × 8 mm, 10 mm × 10

mm, 15 mm × 10 mm, and 20 mm × 10 mm) and is delivered through a 9 Fr or 10.8 Fr catheter. For purposes of EUS-CDS, LAMS with smaller diameters (6 mm, 8 mm, or 10 mm) are preferred, though the 6 mm and 8 mm diameter stents are not currently available in the United States (Figure 1). However, these stents are expensive when compared with plastic and tubular SEMs and may result in complications secondary to inadvertent deployment of the stent by an inexperienced user.

The first successful case of EUS-CDS using LAMS was described by Itoi and Binmoeller[44] in 2014. In 2018, a prospective multicenter study evaluated the long term outcomes of using LAMS for EUS-CDS in 19 patients with unresectable MBO [45]. Successful stent placement was performed in 100% patients and clinical success was achieved in 95%. During the follow up period (median 184 d), 95% of stents remained in good position without migration. RBO was noted in five patients (26%) due to food impaction ($n = 2$), kinking ($n = 1$), tumor ingrowth ($n = 1$) and stent dislodgement ($n = 1$), with four patients requiring reintervention. The risk of stent clogging was attributed to 6mm and 8mm diameter stents used in the study with the authors speculating that a larger stent diameter may reduce this complication. In 2019, a multi-center trial evaluated 67 patients undergoing EUS-CDS with 10 mm diameter EC-LAMS[46]. The technical success rate was 95.5% while early adverse event rate was 6.3%. Clinical success (> 50% decrease in bilirubin) was 100% (40/40) in patients who followed up at four weeks, though 17.4% (7/40) later developed RBO requiring reintervention. The high clinical success observed in this study was probably influenced by limited follow-up, with 27 patients having a follow-up duration of < 4 wk. These patients were not evaluated in terms of clinical success and need for biliary re-intervention.

A systematic review and meta-analysis of thirteen studies and 572 patients who underwent EUS-CDS with PS, SEMs or LAMS showed an overall technical and clinical success rate of 91.9% and an adverse event rate of 14.5%[47]. The most common adverse events were cholangitis, bleeding, bile leak and perforation. Though a trend was observed for improved safety with LAMS over other stents, it did not reach statistical significance. The safety and efficacy of EUS-CDS using EC-LAMS was further evaluated in a subgroup meta-analysis of five studies and 201 patients demonstrating a technical success of 93.8%, clinical success rate of 95.9% and post procedure adverse events rate of 5.6%[48]. The lower rates of adverse events in more recent studies can be attributed to recent advances in EUS technology and growing experience with EUS-BD.

Despite the high technical and clinical success associated with EUS-CDS for distal MBO, the technique was generally reserved for palliative management due to concerns about potential stent inference in patients undergoing curative resection. In 2019, Fabbri *et al*[49] reported five cases of resectable distal MBO where EUS-CDS was utilized as a bridge to surgery following failed ERCP[49]. All five patients underwent successful EUS-CDS, and each subsequently underwent successful pylorus-preserving pancreaticoduodenectomy. The transduodenal LAMS did not impede surgery thereby suggesting that EUS-CDS can be performed even in patients with resectable malignancy. Additionally, in patients with both duodenal and distal biliary obstruction, a one-step procedure with successful EUS-CDS and duodenal stenting has been described[50]. In this case series, a duodenal SEMs was placed during the same procedure as EUS-CDS without need the need to switch the echoendoscope with a duodenoscope or forward viewing endoscope.

EUS-CDS provides a viable alternative for biliary drainage (after unsuccessful ERCP) in patients presenting with distal MBO. However, this procedure cannot be performed in patients with a proximal obstruction. Additionally, GOO inhibiting endoscopic access to the duodenal bulb can be a limiting factor. In such cases, an intrahepatic approach is more often feasible.

EUS-GUIDED HEPATICOGASTROSTOMY

EUS-guided hepaticogastrostomy (EUS-HGS) is a feasible treatment option in patients when transpapillary or transduodenal forms of biliary drainage are not possible. This includes patients with GOO and surgically altered GI anatomy. The technique was first described in 2003 in a patient with a partial gastrectomy with Billroth II reconstruction, in which a transgastric plastic stent was successfully placed into a dilated left intrahepatic duct[51].

With the echoendoscope positioned in the stomach, a dilated left intrahepatic bile duct (segment III) is identified and punctured with a 19-gauge fine-needle aspiration

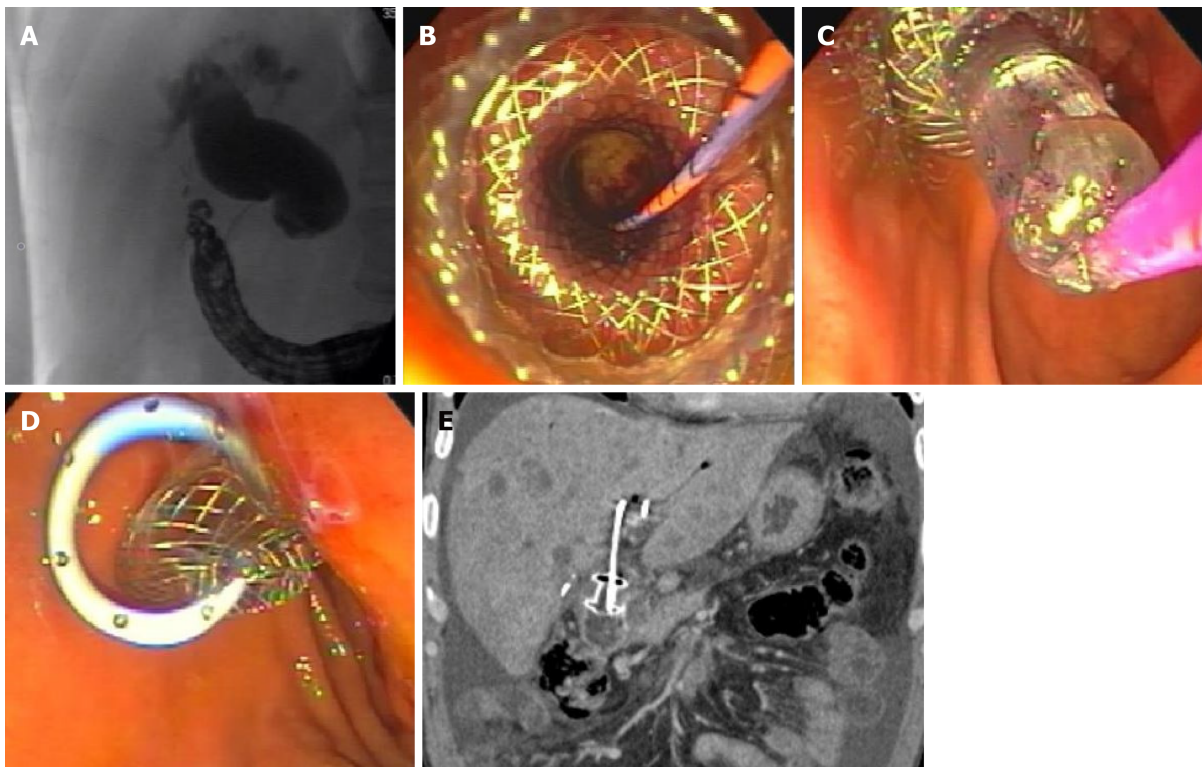


Figure 1 Endoscopic ultrasound-guided choledochoduodenostomy for distal malignant biliary obstruction using an electrocautery-enhanced lumen apposing metal stent. A: Fluoroscopic image showing a dilated bile duct with distal biliary stricture secondary to pancreas head mass; B: Endoscopic image following lumen-apposing self-expanding metal stent (LAMS) deployment in the common bile duct; C: Balloon dilation of LAMS using a wire-guided balloon; D: Endoscopic image with double pigtail stent through the LAMS in the duodenal bulb; E: Computed tomography coronal image showing choledochoduodenostomy with a double pigtail stent through the LAMS. The proximal end of the double pigtail plastic stent is in the left intrahepatic duct.

(FNA) needle. After confirmation of needle placement into the duct by aspiration of bile and cholangiogram, a guidewire is advanced downstream into the distal bile duct, followed by tract dilation and stent placement through the fistulous tract with the distal end of the stent in the intrahepatic bile duct and the proximal end in the stomach [52,53]. In 2017 Oh *et al* [54] set out to determine the ideal biliary access point for successful EUS-HGS [54]. In the study of 129 patients, technical success was achieved in 93% and functional success in 81.4%, while adverse event rate was 24.8%. From data analysis, authors concluded the intrahepatic bile duct diameter at point of puncture should be > 5 mm. Additionally, it was suggested a hepatic portion length (distance from mural wall to punctured bile duct) of 1 to ≤ 3 cm may facilitate successful EUS-HGS.

Despite the high technical success rates associated with this procedure, adverse events with EUS-HGS are not infrequent. These include stent migration with bile peritonitis, bleeding and pneumoperitoneum. Ogura and Higuchi [55] described increased risk of mediastinitis associated with puncture of the segment II radical from the esophagus [55]. Similar to EUS-RV, guidewire manipulation through the intrahepatic bile ducts is a difficult step of the procedure and can result in wire shearing. A “liver impaction technique” has been described in which, after the guidewire is pushed adequately into the peripheral bile duct, the FNA needle is pulled back into the hepatic parenchyma [56]. Authors noted that because the tip of the FNA needle is now within the hepatic parenchyma, shearing while manipulating the guidewire within the biliary system becomes less likely.

Numerous studies have demonstrated increased risk of bleeding with the use of non-coaxial electrocautery for tract dilation. In a prospective study by Park *et al* [57], post procedure adverse events with tract dilation using needle-knife were significantly higher when compared to graded dilation (33% *vs* 7%, $P = 0.02$) [57]. Similar results were seen by Honjo *et al* [58] when comparing dilation with ultra-tapered mechanical dilators *vs* electrocautery dilator [58]. Though the procedure duration was shorter in the electrocautery group, the risk of bleeding was significantly higher. In a 2016 study by Khashab *et al* [36], coaxial and non-coaxial electrocautery for achieving tract dilation were separately analyzed, with increased risk of adverse events associated with non-coaxial electrocautery (OR 3.95, $P = 0.03$) [36].

Choice of stent for EUS-HGS plays an important role in procedural success and safety. As with EUS-CDS, PS have several disadvantages when compared to metal stents including increased risk of clogging (due to smaller diameter) as well as bile leak and bleeding (due to lack of tamponade effect)[33,36,53]. For these reasons, tubular metal stents are favored in EUS-HGS. However, stent migration following EUS-HGS is noted to be a major, and at times fatal, adverse event with the use of FC-SEMS[59,60]. One technique utilized by endoscopists to prevent stent migration is placement of a double pigtail plastic stent inside the metal stent, allowing the pigtails to function as anchors[61]. An intra-scope channel release technique has also been described to prevent this complication[62]. In this method the SEMS is released within the scope channel to minimize the stent length in the abdominal cavity. In a study directly comparing outcomes in patients undergoing EUS-HGS using either intra-scope ($n = 21$) or extra-scope ($n = 20$) channel release technique, it was observed that the intra-scope group had significantly shorter distance between the hepatic parenchyma and the stomach wall (0.66 ± 1.25 vs 2.52 ± 0.97 , $P < 0.05$) following stent placement[63]. Adverse events, including stent migration, were only noted in the extra-scope channel group, and the authors concluded the intra-scope release technique was useful for prevention of stent migration. LAMS, while appropriate for use in EUS-CDS, are not suitable for transhepatic drainage.

The use of tubular FC-SEMS for EUS-HGS can result in segmental cholangitis or liver abscess secondary to obstruction of peripheral bile ducts. A prospective preliminary feasibility study by Umeda *et al*[64] in 2015 evaluated the outcomes of a newly designed 8 Fr single pigtail plastic stent for EUS-HGS[64]. The stent had a tapered distal tip, with four flanges and pigtail anchor to prevent proximal and distal stent migration. There were no apertures in the middle part of the stent, thereby decreasing risk of bile leak into the peritoneal cavity. Twenty-three cases were performed using this stent with high technical (100%) and clinical (100%) success reported. Adverse events were noted in 17.4% (comparable to conventional PS), and re-occlusion rate was 13.7% after a median follow-up of 5 mo.

In an effort to minimize the risk of bile leak following fistula dilation, Park *et al*[65] performed a randomized control trial to evaluate the feasibility and safety of a novel dedicated device for one-step EUS-BD[65]. Sixteen patients underwent EUS-BD using a dedicated stent introducer with a modified hybrid metal stent (DH group). The stent introducer (DEUS, Standard Sci Tech, Seoul, South Korea) had a 3 Fr catheter with a 4 Fr tapered metal tip for the puncture of the intestine and liver without the need for tract dilation. The outer sheath of the delivery catheter was 7 Fr. A modified hybrid metal stent with an UC proximal end and covered distal portion was preloaded into the catheter. A conventional 8.5 Fr biliary metal stent introducer with a fully covered metal stent was used in the remaining 16 patients (FC group). Though the procedure duration was significantly shorter in the DH group, the rate of adverse events between the two groups did not reach statistical significance.

In 2017 Cho *et al*[66] reported long term outcomes of a novel hybrid metal stent used to perform EUS-HGS in 21 patients[66]. This hybrid metal stent (Standard Sci Tech Inc., Seoul, South Korea) had a distal covered portion (3.5 cm in length) to prevent bile leak and a proximal UC portion (1.5 to 6.5 cm in length) to decrease the likelihood of cholangitis from intrahepatic biliary obstruction. The proximal and distal anchoring flaps on the covered portion prevented stent migration. The hybrid stents used in this study measured 8 mm or 10 mm in diameter and ranged from 5 cm to 10 cm in length. High technical (100%) and clinical (85.7%) success was reported, with an early adverse event rate of 19%. Stent migration was not observed in the follow-up period, though stent occlusion requiring reintervention occurred in 10 (47.6%) patients after a median of 53.5 d. A retrospective study of 110 patients who underwent EUS-HGS with a long, partially covered (30% UC, 70% covered) metal stent was published by Nakai *et al*[67] in 2020[67]. The authors reported high technical (100%) and functional (94%) success with no reported cases of stent migration. However, 33% of patients eventually suffered RBO requiring re-intervention due to the hyperplastic ingrowth of the UC flange. In this study a shorter stent was associated with shorter time until RBO, and the authors recommended a 10 cm or longer metal stent to prolong stent patency.

In 2015 Ogura *et al*[68] performed a retrospective study to examine potential predictors of stent patency[68]. EUS-HGS using a metal stent (of varying lengths) was performed in 51 patients, with each patient undergoing computed tomography imaging the following day to measure the stent length in the stomach. It was noted that patients with intraluminal stent length < 3 cm had a shorter stent patency compared to patients in whom the stent length was > 3 cm (mean 52 d in < 3 cm vs mean 195 d in > 3 cm). In an effort to prolong stent patency, some endoscopists have utilized a technique combining EUS-HGS with EUS-AG stent placement[69]. Imai *et al*

[70] performed a retrospective study comparing outcomes in patients with MBO treated with EUS-HGS alone (Group A, $n = 42$) versus combined EUS-HGS and EUS-AG (Group B, $n = 37$) [70]. Technical success was higher in Group A (97.6% *vs* 83.8%) while clinical success was equal in both groups (90.2% *vs* 90.3%). Though there were no significant differences noted in duration of stent patency and number of reinterventions between the two groups, group A patients had a higher rate of adverse events (26.1 *vs* 10.8%, $P = 0.03$). Of note, bile leak was noted in seven patients in group A, and only one patient in group B.

In addition to achieving biliary drainage in the setting of MBO, EUS-HGS can also be used to manage benign biliary diseases (such as choledocholithiasis, hepatolithiasis and biliary stricture) in patients with inaccessible papilla [71,72] (Figure 2). In 2018 James *et al* [73] performed a retrospective review of 20 patients with surgically altered GI anatomy who underwent EUS-hepaticocenterostomy (EUS-HE) for management for benign biliary disease [73]. Indications included CBD stones ($n = 8$), biliary stricture ($n = 11$) and bile leak ($n = 1$). Technical success was achieved in 100% patients, with 90% (18/20) then undergoing antegrade biliary therapy for stone clearance or treatment of biliary stricture. Patients underwent a mean of 2.7 procedures until resolution of their condition, with successful removal of the EUS-HE stent in 17/20 patients after a mean of 91 d.

A complete hilar biliary obstruction (HBO) presents a limitation for EUS-HGS, as drainage from the left intrahepatic duct does not necessarily relieve a right sided obstruction. In 2013 Park *et al* [74] described a technique of direct puncture of the right hepatic duct from the bulb of the duodenum with transluminal stent placement, forming a hepaticoduodenostomy [74]. Ogura *et al* [75] reported success using a novel “bridge” technique which involves placement of a stent across the HBO, thus connecting the right and left intrahepatic, followed by EUS-HGS [75]. Both techniques are challenging and only a small number of cases performed in referral centers have been reported to date [76]. In addition, EUS-HGS may be contraindicated in patients with large abdominal ascites (preventing fistula formation with increased risk of stent migration) and unresectable gastric cancer.

EUS-CDS VS EUS-HGS

EUS-CDS and EUS-HGS are both effective in management of biliary obstruction following ERCP failure. EUS-HGS however, may be associated with a slightly higher rate of adverse events, likely due to a number of factors including the precise puncture of smaller caliber intrahepatic bile ducts through the liver parenchyma as well as increased risk of pneumoperitoneum and bile leakage in the peritoneal cavity.

A retrospective study directly comparing EUS-CDS and EUS-HGS in 121 patients (60 CDS and 61 HGS) showed a high technical (93.3% CDS and 91.8% HGS) and clinical (85.5% CDS and 82.1% HGS) success with both techniques, with a similar rate of adverse events (13.3% CDS *vs* 19.67% HGS, $P = 0.37$) in both groups [36]. The stent patency duration between the two groups was not statistically significant ($P = 0.228$). Similar results were seen in a meta-analysis of 434 patients (208 HGS and 226 CDS) with comparable technical success (93.7% HGS and 94.1% CDS), clinical success (84.5% HGS and 88.5% CDS) and adverse events (OR = 0.97, 95%CI: 0.60-1.56) in both groups [77]. However, in a separate meta-analysis of 686 patients (283 CDS and 403 HGS) adverse events were noted to be significantly higher in the EUS-HGS group (29% HGS and 20% CDS, $P = 0.01$) [78].

In the end, the choice between EUS-CDS or EUS-HGS often comes down to a patient-by-patient basis, with a decision based on patient anatomy, site of obstructing lesion, operator expertise and location of biliary dilation. EUS-CDS is most suitable in patients with distal MBO. However, it is not feasible in patients with proximal MBO. EUS-HGS can be utilized in such patients, as well as those with surgically altered GI anatomy. Nevertheless, if intrahepatic ductal dilation is not present, EUS-HGS is not a practical option.

EUS-GUIDED GALLBLADDER DRAINAGE

EUS-guided gallbladder drainage (EUS-GBD) allows for direct internal decompression of the gallbladder in patients presenting with acute cholecystitis who are poor surgical candidates. The technique was first described by Baron and Topazian [79] in 2007. Since then, numerous studies have demonstrated success with this technique using

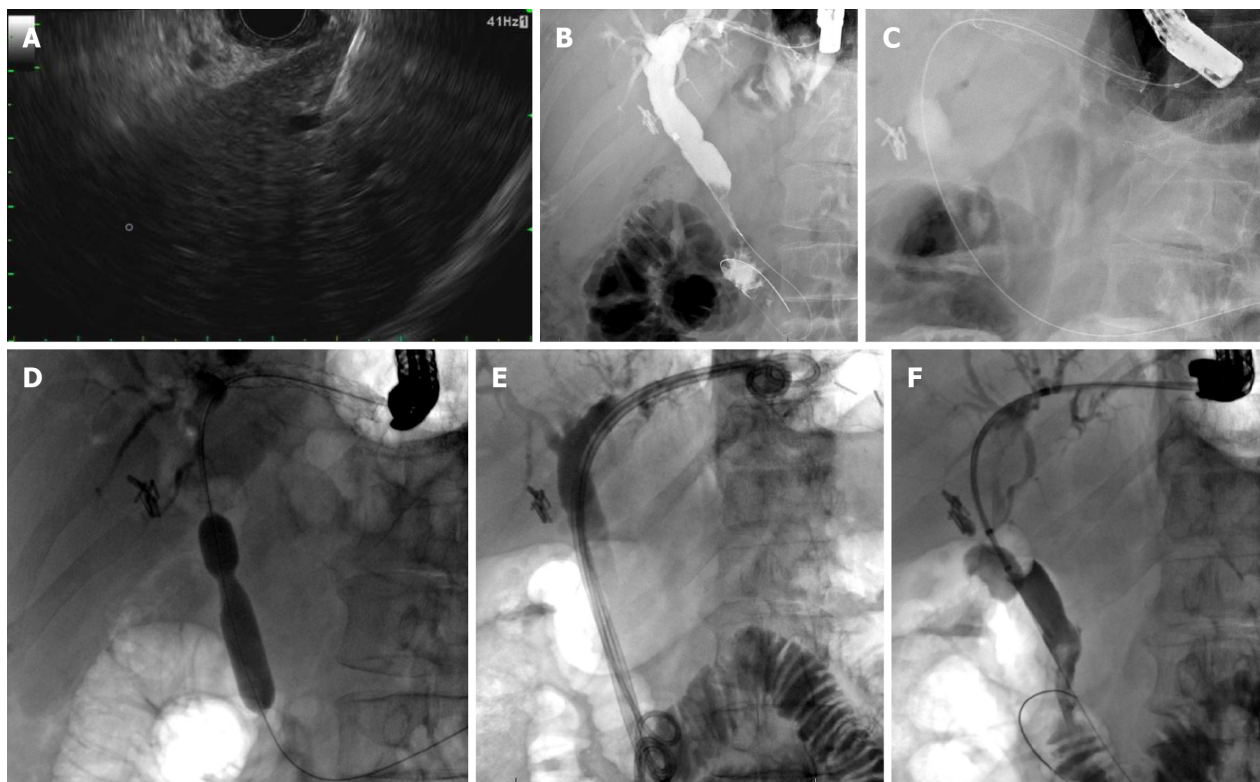


Figure 2 Endoscopic ultrasound-guided hepaticogastrostomy for benign distal biliary stricture in a patient with history of roux-en-Y gastric bypass surgery. A: Endoscopic ultrasound-guided puncture of a dilated B3 radical with a 19-gauge needle; B: Fluoroscopic image showing a dilated bile duct with distal biliary stricture; C: Fluoroscopic image showing placement of a fully covered hepaticogastrostomy metal stent; D: Antegrade balloon dilation of the distal bile duct stricture using a wire-guided balloon; E: Successful placement of four 7 Fr × 18 cm double pigtail biliary stents with the distal end past the ampulla in the small bowel and the proximal end in the stomach; F: Occlusion cholangiogram following removal of plastic hepaticogastrostomy stents showing resolution of distal bile duct stricture with free flow of contrast into the small bowel.

both transgastric and transduodenal approaches[80,81].

In 2013, Itoi *et al*[82] performed EUS-GBD using LAMS for management of obstructive jaundice secondary to distal MBO[82]. Following this, Imai *et al*[83] published a case series of 12 patients with unresectable distal MBO who underwent EUS-GBD following failed ERCP with high technical (100%) and functional (91.7%) success[83]. Adverse events were noted in 16.7% patients, with stent dysfunction occurring in 8%. A recent multicenter retrospective study of 28 patients undergoing EUS-GBD for distal MBO reported similar high technical (100%) and clinical (93%) success rates[84]. Delayed adverse events requiring reintervention occurred in 17.9% (5/28) patients. These included three patients with food impaction leading to acute cholecystitis and two patients with delayed bleeding. No perforation or stent migration was observed in this study.

In summary, EUS-GBD can be utilized in management of patients with distal MBO when standard ERCP and other forms of EUS-BD (EUS-CDS, EUS-HGS and EUS-RV) are not technically feasible. Cystic duct patency should always be evaluated prior to performing this procedure for biliary drainage. The biliary obstruction should be distal to the cystic duct takeoff to allow for proper biliary decompression[85] (Figure 3).

EUS-DIRECTED TRANSGASTRIC ERCP

EUS-directed transgastric ERCP (EDGE) is a valuable alternative to enteroscopy-assisted ERCP (e-ERCP) and laparoscopy-assisted ERCP (LA-ERCP) in patients with roux-en-Y gastric bypass (RYGB) anatomy requiring pancreatobiliary intervention. Under EUS guidance, the excluded stomach can be identified from the remnant gastric pouch or jejunum. Following puncture with a 19-gauge needle, a guidewire is advanced in the excluded stomach, followed by LAMS placement over the guidewire to create a gastrogastic or jejuno gastric fistula. A duodenoscope is then passed through the LAMS and advanced to the major papilla to perform standard ERCP.

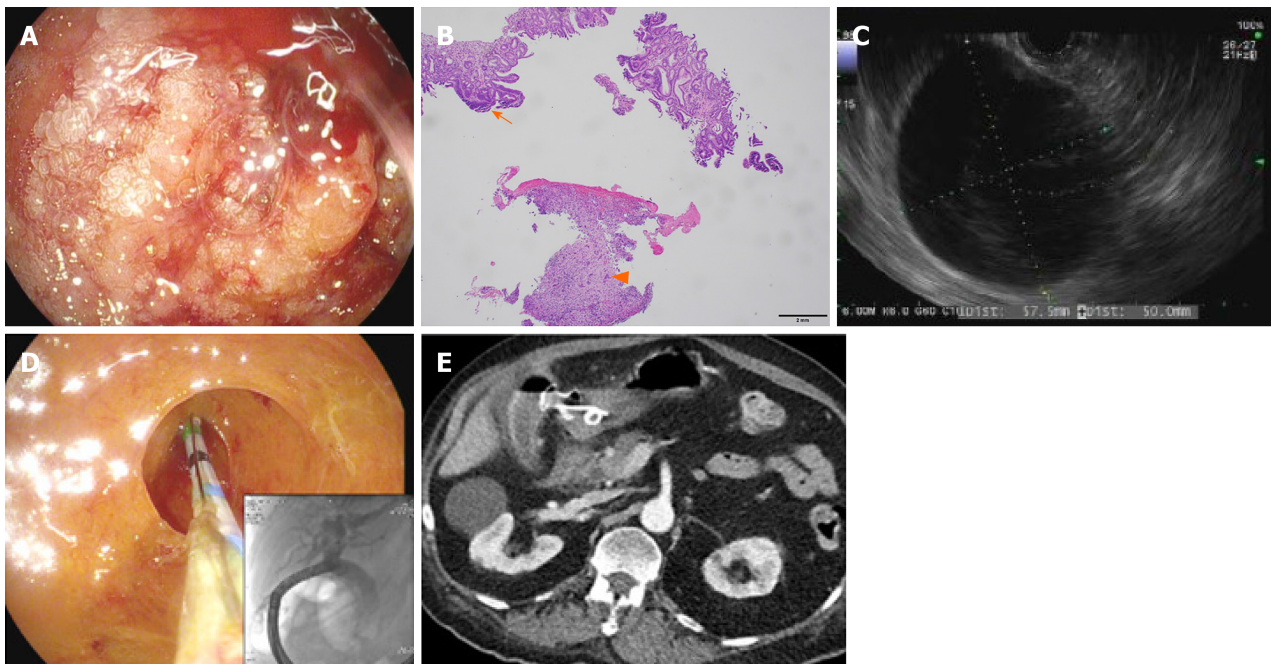


Figure 3 Endoscopic ultrasound-guided gallbladder drainage for distal malignant biliary obstruction secondary to duodenal adenocarcinoma using an electrocautery-enhanced lumen apposing metal stent. A: Duodenal adenocarcinoma involving the duodenal sweep causing luminal narrowing; B: Adenocarcinoma (arrow heads) arising in a background of adenoma (arrow) with focal high-grade dysplasia (H&E stain); C: Endoscopic ultrasound image displaying distended gallbladder; D: Cholecystoscopy [post lumen-apposing self-expanding metal stent (LAMS) placement] with contrast injection via cystic duct opening opacifying the biliary tree showing a patent cystic duct; E: Post-procedural computed tomography scan displaying double pigtail stent and LAMS in place between gastric antrum and gallbladder.

Intervention can be performed during the index procedure or in a subsequent session. Once access to the duodenum and papilla is no longer required, the LAMS can be removed, and fistula closed using argon plasma coagulation, endoscopic clips, or endoscopic sutures (Figure 4).

The EDGE procedure was first described by Kedia *et al* [86] in 2014 [86]. In 2017, a multicenter study on 16 patients undergoing EDGE procedure reported a high technical (100%) and clinical (91%) success, with stent dislodgement occurring in 19% patients [87]. A recent multicenter retrospective study by Runge *et al* [88] reported long-term outcomes in 178 patients following EDGE procedure [88]. Technical success was achieved in 98% cases with adverse events occurring in 28 (15.7%) patients. The most common adverse events noted were LAMS misdeployment or migration ($n = 13$) and perforation ($n = 6$). Follow up endoscopy or upper GI imaging was completed in 90 patients (following stent removal) with nine patients (10%) showing persistent fistula. Fistula closure was successful in all five patients who then returned for follow up.

A 2018 study by Bukhari *et al* [89] compared outcomes of EDGE *vs* e-ERCP [89]. Technical success was higher in patients undergoing EDGE procedure (100% EDGE *vs* 60% e-ERCP) with a significantly shorter procedure time noted in this group (49.8 min EDGE *vs* 90.7 min e-ERCP, $P < 0.001$). Adverse events were similar in both groups. Outcomes of EDGE and LA-ERCP were compared in a 2019 study by Kedia *et al* [90] with similar success rates (96.5% EDGE and 97.7% LA-ERCP) and adverse events (24% EDGE and 19% LA-ERCP) in both groups [90]. However, shorter procedure times ($P < 0.00001$) and lengths of hospital stay ($P < 0.00008$) were noted in the EDGE group.

LAMS dislodgement during ERCP is a major adverse event which can result in perforation if the fistula tract has not yet matured. To avoid this, some endoscopists recommend performing EDGE in two steps, allowing fistula maturation following LAMS placement prior to performing ERCP [89]. Alternatively, a single-stage EDGE can be performed by securing LAMS with an endoscopic stitch or over-the-scope clip [91]. Persistent fistula between the gastric remnant and excluded stomach and subsequent weight gain is a worrisome complication of the EDGE procedure. However, most major studies have not shown any significant weight gain associated with the procedure [88-90]. Given the reported safety profile and high success rate of the EDGE procedure, it can be used as a first line therapy in RYGB patients requiring biliary interventions.

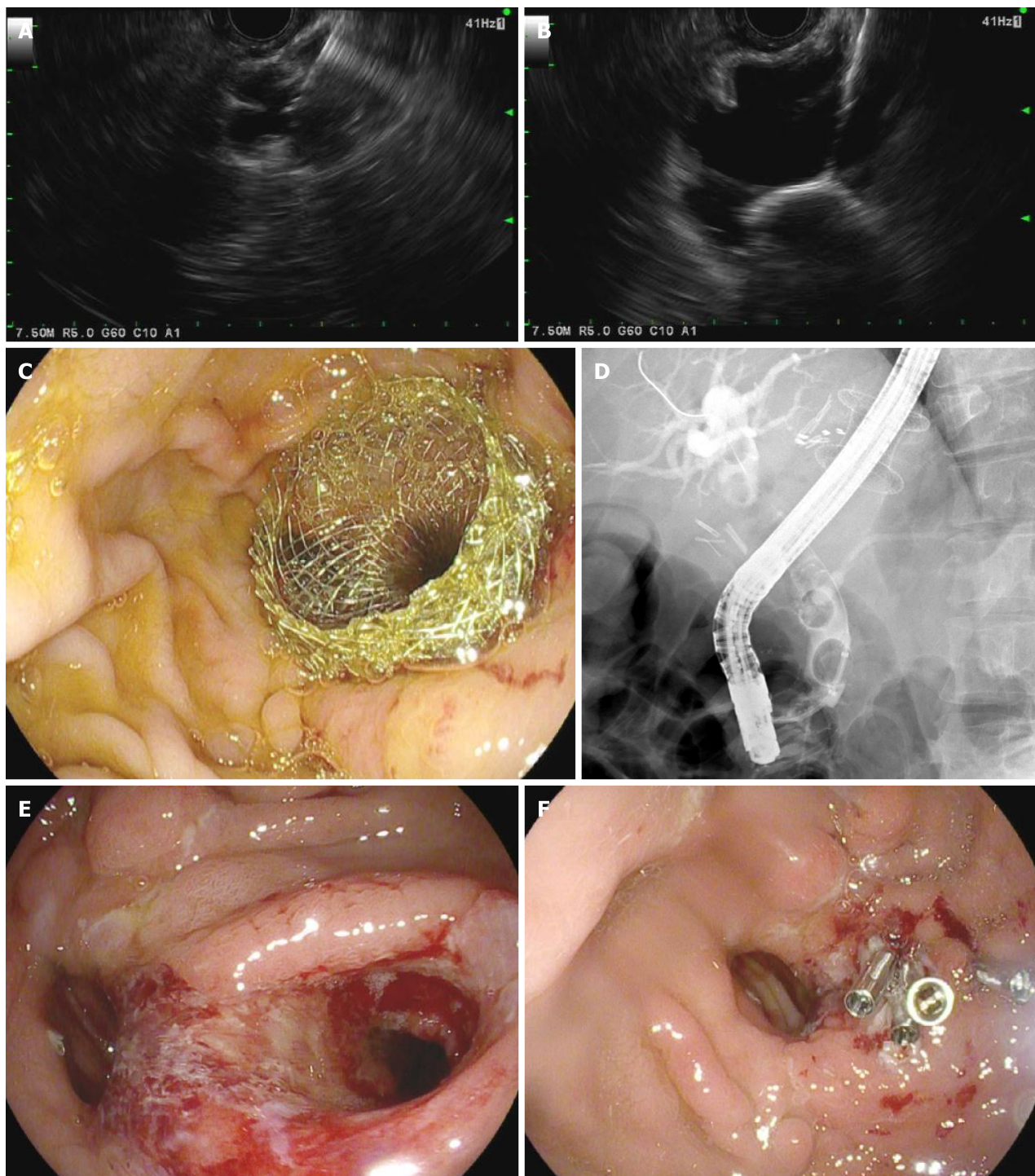


Figure 4 Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiography for choledocholithiasis in a patient with history of roux-en-Y gastric bypass surgery. A: Endoscopic ultrasound-guided puncture of excluded stomach using a 19-gauge needle; B: Endoscopic ultrasound showing deployment of proximal flange of lumen-apposing self-expanding metal stent (LAMS) in the excluded stomach; C: Endoscopic image showing distal flange of LAMS in the gastric pouch; D: Fluoroscopic image of endoscopic retrograde cholangiopancreatography through LAMS showing multiple stones in the common bile duct; E: Gastrogastric fistula seen following LAMS removal; F: Successful closure of gastrogastric fistula using argon plasma coagulation and clips.

CONCLUSION

Over the past two decades, EUS-BD has continued to evolve and is more frequently utilized in managing patients with benign and malignant biliary diseases at tertiary care centers with EUS expertise (Figure 5). The procedure has a high success rate and fewer complications than other forms of biliary drainage including PTBD and surgical bypass, making it a preferred alternative following failed ERCP. However, a significant learning curve is associated with this procedure, with literature suggesting experienced endoscopists requiring over 30 cases to become efficient and nearly 100

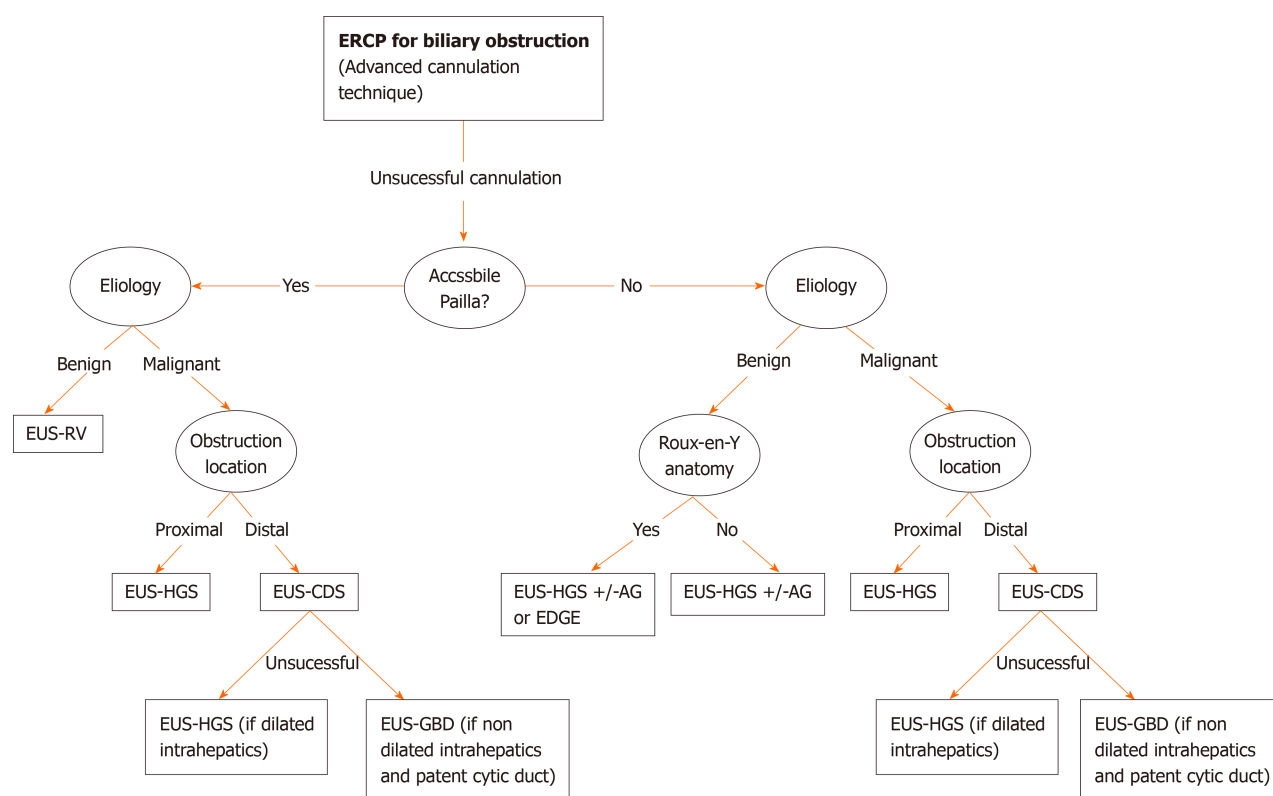


Figure 5 Proposed algorithm for endoscopic ultrasound-guided biliary drainage for biliary obstruction following failed endoscopic retrograde cholangiopancreatography. EUS: Endoscopic ultrasound; HGS: Hepaticogastrostomy; CDS: Choledochoduodenostomy; ERCP: Endoscopic retrograde cholangiopancreatography; EDGE: EUS-directed transgastric ERCP; GBD: Gallbladder drainage; RV: Rendezvous.

cases before mastering these techniques[92]. In addition, there is insufficient evidence on the route of choice, and patients with biliary obstruction should be evaluated on a case-by-case basis by an experienced therapeutic endoscopist backed by a multidisciplinary team. The development of novel LAMS has led to improved outcomes in patients undergoing EUS-CDS. Further innovations in the development of EUS-BD specific tools coupled with standardization of techniques will likely lead to improved safety. Future prospective clinical trials are needed to better evaluate outcomes and further advance this rapidly evolving field of interventional EUS.

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Retrospective Study

Thoracoscopic esophagectomy is related to better outcomes in early adenocarcinoma of esophagogastric junction tumors

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Author contributions: Takeda FR did acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; Obregon CA, Ribeiro Jr U and Sallum RAA did analysis and interpretation of data, revising the article; Navarro, YP: analysis and interpretation of data, revising the article; de Moura DTH and Cecconello I analysis of data, interpretation of data, drafting the article, revising the article, final approval.

Institutional review board

statement: This is a retrospective review performed at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and Instituto do Câncer do Estado de São Paulo (ICESP). As this is a retrospective analysis, the Ethics committee of both institutions exempted the need for approval.

Informed consent statement:

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Abstract

BACKGROUND

Thoracoscopic esophagectomy is related to an extended lymphadenectomy, and a high number of retrieved lymph nodes, compared to the transhiatal approach; however, its association with an improvement in overall survival (OS) is debatable.

AIM

To compare thoracoscopic esophagectomy with transhiatal esophagectomy in patients with adenocarcinoma of the esophagogastric junction (AEGJ) in terms of survival, number of lymph nodes, and complications.

METHODS

In total, 147 patients with AEGJ were selected retrospectively from 2002 to 2019, and divided into Group A for thoracoscopic esophagectomy, and group B for transhiatal esophagectomy. OS, disease-free survival, postoperative complications, and number of nodes, were similarly evaluated.

RESULTS

One hundred and thirty (88%) were male; the mean age was 64 years. Group A had a mean age of 61.1 years and group B 65.7 years ($P = 0.009$). Concerning the extent of lymphadenectomy, group A showed a higher number of retrieved lymph nodes (mean of 31.89 ± 8.2 vs 20.73 ± 7 ; $P < 0.001$), with more perioperative complications, such as hoarseness, surgical site infections, and respiratory complications. Although both groups had similar OS rates, subgroup analysis showed better survival of transthoracic esophagectomy in patients with earlier diseases.

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors deny any conflict of interest.

Data sharing statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Manuscript source: Invited manuscript

Specialty type: Surgery

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 18, 2021

Peer-review started: February 18, 2021

First decision: March 14, 2021

Revised: March 21, 2021

Accepted: July 14, 2021

Article in press: July 14, 2021

Published online: August 16, 2021

P-Reviewer: Laracca GG

S-Editor: Zhang H

L-Editor: A

P-Editor: Wang LYT

CONCLUSION

Both methods are safe, having similar morbidity and mortality rates. Transthoracic thoroscopic esophagectomy allows a more extensive resection of the lymph nodes and may have better oncological outcomes during earlier stages of the disease. Prospective studies are warranted to better evaluate these findings.

Key Words: Adenocarcinoma; Esophagogastric junction; Transhiatal; Thoroscopic; Lymph nodes; Surgery

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Core Tip: The type of access during esophagectomy to adenocarcinoma of esophagogastric junction tumor is on debate. Thoroscopic esophagectomy produces higher numbers of retrieved lymph nodes than transhiatal esophagectomy but is associated with more perioperative complications. The relationship between lymphadenectomy's extension and survival outcomes is debatable. We compared both access and found better survival in early staging of patients treated by thoroscopic esophagectomy, probably due to the extension of lymphadenectomy and acceptable complication rate. These findings reveal a new place of thoroscopic esophagectomy for adenocarcinoma of the esophagogastric junction tumor in the multimodal era.

Citation: Takeda FR, Obregon CA, Navarro YP, Moura DTH, Ribeiro Jr U, Aissar Sallum RA, Cecconello I. Thoroscopic esophagectomy is related to better outcomes in early adenocarcinoma of esophagogastric junction tumors. *World J Gastrointest Endosc* 2021; 13(8): 319-328

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/319.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.319>

INTRODUCTION

Esophageal cancer is one of the most lethal neoplasms worldwide (with about 17000 new cases per year), and the sixth leading cause of cancer deaths (286000 deaths per year)[1]. The most frequent histologic type of esophageal neoplasm is squamous cell carcinoma, responsible for 76% of cases, followed by adenocarcinoma[2] in Eastern countries. In our institution, adenocarcinoma increased from 15% to 32.5% over the last thirteen years[3]. In the same way, the prevalence of adenocarcinoma of the esophagogastric junction (AEGJ) is rising in Western countries, mostly due to the higher prevalence of risk factors such as obesity[4].

The topographic distribution of metastatic lymph nodes of AEGJ varies according to the Siewert classification. In Siewert type I, the main lymphatic drainages are predominantly in the middle and lower mediastinum; in type II, in the lower mediastinum, thoracoabdominal transition, and abdominal part; and in type III, almost entirely abdominal[5]. Regarding surgical treatment, Siewert type II leads the indication for the transhiatal approach, and Siewert type I leads for the transthoracic approach[6,7]. Despite controversy over access to esophagectomy, transthoracic access is preferred by several Western surgeons[8-10], partly because most advocate an infracarinal lymphadenectomy[11]. However, the addition of minimally invasive techniques, associated with a lower number of postoperative complications and morbidity rates, makes transthoracic esophagectomy by thoracoscopy one of the main options. Yet, extensive radical resection has not shown better survival than transhiatal en bloc esophagectomy with extended lymphadenectomy[12]. Some studies find that the extremely invasive procedure leads to an increase in morbidity and mortality[13,14], which might interfere with overall survival (OS).

This study aimed to analyze the results of AEGJ surgical treatment, comparing transhiatal esophagectomy and transthoracic esophagectomy access by thoracoscopy, including outcomes such as complications and mortality rates, and extension of lymphadenectomy as represented by the number of resected lymph nodes.



MATERIALS AND METHODS

This is a retrospective study following the STROBE Statement Checklist analysing patients with a histological diagnosis of AEGJ, Siewert I and II types, who underwent surgical treatment [transthoracic esophagectomy by thoracoscopy (group A) (Figure 1A) and transhiatal esophagectomy (group B) (Figure 1B)] between 2002 and 2019 at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and Instituto do Câncer do Estado de São Paulo. As this is a retrospective analysis, the Ethics committee of both institutions exempted the need for approval.

The following epidemiological data were analyzed and compared between group A and B: age, gender, body mass index, preoperative functional assessment by the Zubrod scale (Eastern Cooperative Oncology Group), and a relevant personal medical history (diabetes, cardiovascular disease, *etc.*).

Surgical treatment

Transhiatal esophagectomy: This procedure involves a dissection of the combined cervical and abdominal esophagus without opening the thorax. Improved by Pinotti [15], with transection of the diaphragm, it allowed dissection under direct view of almost the entire mediastinum, thereby avoiding the inconvenience of blunt dissection of the esophagus.

After opening the diaphragm, the infracarinal lymphadenectomy is performed around the bilateral pleural, added to resection of lymph nodes around the hepatic artery, left gastric artery and vein, and the celiac trunk. In the abdominal section, the stomach is released in the great curvature, preserving the arch from the gastroepiploic vessels. The stomach is transposed into the cervical region through the posterior mediastinum, with cervical gastroplasty performed (preparation of the isoperistaltic gastric tube) with linear staplers and oversuturing.

Transthoracic thoracoscopic esophagectomy: After selective intubation of the left bronchus, the patient is placed in a prone position, along with five trocars. The first one at 12 mm is introduced at the inferior limit of the right scapula. The other four trocars are positioned under direct visualization (after positive intrathoracic insufflation of 8 mmHg of CO₂).

Three other trocars (two 10 mm and one 5 mm) are arranged with the first in a semicircular line from the medial border of the scapula to the posterior right costal border. Finally, the fifth trocar is positioned at the midpoint of this line, next to the spine.

Dissection of the esophagus is performed from the lower to upper mediastinum. Extensive lymphadenectomy takes place: periesophageal, periaortic, supradiaphragmatic, and pericardial lymph nodes are dissected. The right and left infracarinal lymph nodes are resected, which exposes the right and left bronchi to their origin in the carina.

In order to facilitate esophageal mobilization and the lymphadenectomy, the azygos vein is ligated and transected (preferentially with a laparoscopic stapler).

After dissection, the right pleural space is drained, and the trocars are withdrawn. The patient is placed supine in order to proceed with the abdominal part (which occurs similarly to that described in the open transhiatal esophagectomy).

Outcomes

The main outcomes of this study include resected lymph nodes, complications and deaths. Once the surgical specimen is removed, the lymph nodes are immediately dissected by the surgeon and separated based on lymph node stations. This material is sent for anatomopathological study (N), together with the surgical specimen, each in formaldehyde. The resected lymph nodes (LDs) for patients in groups A and B were compared. The lymph nodes affected (LA) and the status of the dissected and affected (LD/LA) in each group were evaluated. Postoperative complications analyzed include cervical fistulae, chylothorax, respiratory disorders (pneumonia, atelectasis, pleural effusions, and respiratory failure), hoarseness (paralysis or paresis of vocal cords), and infection (mediastinal collections and abscesses).

Statistical analysis

Data were reported as number (%) or mean \pm SD. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. Survival outcomes were compared using the Kaplan-Meier method and the log-rank test. The Cox proportional hazards model was used to identify relevant prognostic factors, with significant covariables from the univariate

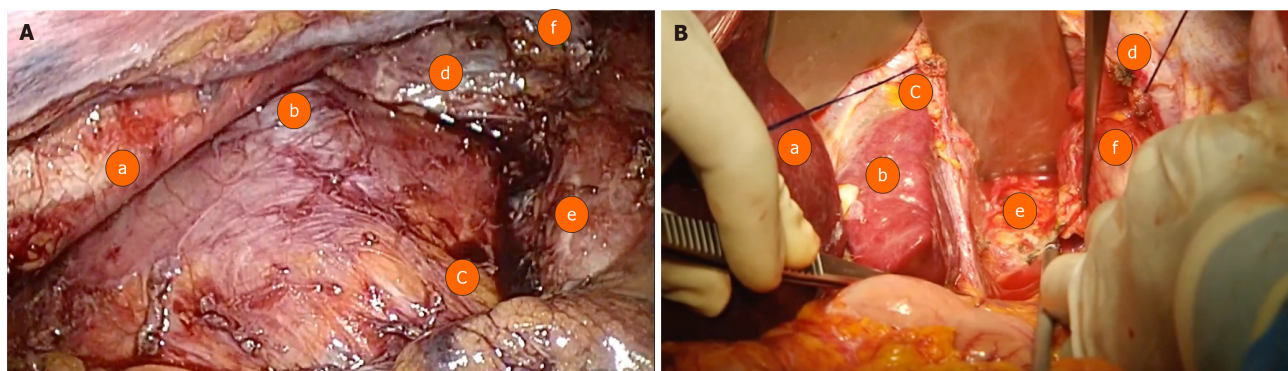


Figure 1 Esophagectomy approaches for patients with esophagogastric junction adenocarcinoma. A: Final mediastinal aspect after esophagectomy with lymphadenectomy by thoracoscopic transthoracic esophagectomy technique for patients with esophagogastric junction adenocarcinoma (a: Thoracic aorta; b: Left pulmonary vein; c: Right pulmonary vein; d: Left bronchi's; e: Right bronchus; and f: Azygous vein); B: Final mediastinal aspect after esophagectomy with lymphadenectomy by transhiatal esophagectomy technique for patients with esophagogastric junction adenocarcinoma (a: Left hepatic lobe; b: Caudate hepatic lobe; c: Right diaphragmatic pillar; d: Left diaphragmatic pillar; e: Thoracic aorta; and f: Distal esophagus).

analyses selected for the multivariate model. The results were reported as hazard ratios and 95% CIs. Differences were considered statistically significant at P -values of < 0.05 , and all analyses were performed using IBM SPSS software (version 20, IBM Corp., Armonk, NY, United States).

RESULTS

Fifty-four patients underwent transthoracic esophagectomy by thoracoscopy (group A) and 93 transhiatal approach (group B). Forty-seven patients from group A (87.0%) and forty-three patients from group B (46.2%) received neoadjuvant treatment (chemotherapy associated with radiotherapy as needed).

Epidemiological data are shown in Table 1. Age was higher in patients undergoing transhiatal esophagectomy ($P = 0.009$); however, the other parameters analyzed were similar.

Complications and mortality

The absolute number of respiratory complications was higher in patients undergoing thoracoscopy esophagectomy, although no significant difference was observed between groups A and B. The most frequent respiratory complications involved segmental atelectasis. One patient experienced a residual pneumothorax, probably related to low flow of the peripheral air fistula.

Temporary paralysis of vocal cords, translated by hoarseness and surgical site infections, were more frequent in group A (both with $P = 0.017$).

Most infectious complications were related to atelectasis, complicated by bronchopneumonia (with diagnosis made through radiological findings, laboratory tests, and clinical evaluation).

Mortality within days was similar between the two groups. In group A, one death was reported due to cervical fistula with drainage to the mediastinum, while another was due to acute myocardial infarction. In group B, two deaths were related to cardiogenic shock. One patient died of massive bronchoaspiration, and one due to a fistula to the mediastinum.

Table 2 shows the main complications and mortality observed for the total number of patients in both groups.

Resected lymph nodes

In group A, 15 to 73 lymph nodes were resected (mean 31.89 ± 8.2) and 1 to 25 Lymph nodes were affected (mean 3.96 ± 1.7). In Group B, 14 to 48 Lymph nodes were resected (mean 20.73 ± 7); 1 to 14 Lymph nodes were affected (mean 4.25 ± 1).

The number of resected lymph nodes in group A was higher ($P < 0.001$). There was no difference in the number of lymph nodes affected ($P = 0.721$) or the DL/AL ratio in both groups ($P = 0.666$). The data regarding resected lymph nodes are summarized in Table 3.

Table 1 Epidemiological characteristics of the total number of patients with adenocarcinoma of the esophagogastric junction by type of operation

Characteristics		Group		Total	P value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, n (%)	n = 93, n (%)	n = 147, n (%)	
Gender	Female	6 (11.1)	11 (11.8)	17 (11.6)	0.896 ¹
	Male	48 (88.9)	82 (88.2)	130 (88.4)	
Age (yr)	mean ± SD	61.11 ± 9.03	65.72 ± 10.73	64.03 ± 10.35	0.009 ²
	Mean (vmin-vmax)	62.50 (37-84)	65.00 (36-94)	64.00 (36-94)	
BMI class	BMI < 25 kg/m ²	46 (85.2)	78 (83.9)	124 (84.4)	0.833 ¹
	BMI > 25 kg/m ²	8 (14.8)	15 (16.1)	23 (15.6)	
Pre-surgical ECOG§	Score 0	50 (92.6)	79 (84.9)	129 (87.8)	0.173 ¹
	Score 1	4 (7.4)	14 (15.1)	18 (12.2)	
Diabetes	No	39 (72.2)	67 (72.0)	106 (72.1)	0.981 ¹
	Yes	15 (27.8)	26 (28.0)	41 (27.9)	
Cardiovascular diseases	No	21 (38.9)	34 (36.6)	55 (37.4)	0.778 ¹
	Yes	33 (61.1)	59 (63.4)	92 (62.6)	

¹Pearson's chi-square test.²Student's *t*-test.

§ Score 0: Totally active and restricted activities; and Score 1: Restricted physical activities, but walking e apt to perform light work activities. vmin: Minimum value; vmax: Maximum value.

Long-term results

With regard to OS and disease-free survival (DFS), there is no statistically significant difference between groups (Table 4). However, when results are analyzed by clinical stage, longer survival is observed in patients with earlier disease (up to stage 2B), undergoing thoracoscopic esophagectomy ($P = 0.001$, Figure 2 and Table 4).

Other factors associated with OS in the univariate analysis include transhiatal approach, grade 3, metastatic lymph node, pT3/4, and lymphatic invasion in the tumor specimen. The multivariable analysis demonstrated better results related to transhiatal access in early staging tumors, hazard ratio 1.73 (95% CI: 1.00-2.99, $P = 0.049$). Factors associated to DFS were: transhiatal approach, metastatic lymph node, pT3/4, and lymphatic invasion in the tumor specimen (Table 4).

DISCUSSION

AEGJ is one of the neoplasms with the highest global rate of increased incidence through the last years, associated with risk factors such as obesity and gastroesophageal reflux disease[16].

In Brazil and many Western countries, it is still a disease with a poor prognosis, mainly because about 65% are T3 or T4 at the time of diagnosis. Recently, Tustumi *et al* [3] published a cross-sectional study performed in our center, in which more than 550 patients with esophageal cancer had an OS rate of 20.2% for AEGJ (types I, II, and III). The percentage of curative-intent surgery in AEGJ was 30.4%, with a mean survival rate of 58% after five years follow-up.

Several factors associated with treatment contributed to improved survival of patients with AEGJ in recent years, among them, neoadjuvant treatment stands out[7, 17]. Based on the most recent data, neoadjuvant chemotherapy and radiotherapy (similar to the CROSS trial) were performed for esophageal tumors and for both pre- and postoperative chemotherapy in patients with predominantly gastric tumors.

Regarding surgical approach, transhiatal esophagectomy was initially performed by Akiyama *et al*[18] in Japan in 1975; Orringer *et al*[19] in the United States in 1978; and Pinotti[15] in Brazil in 1976, which was the preferred approach for AEGJ. Several

Table 2 Postoperative complications and mortality rates of the total number of patients with adenocarcinoma of the esophagogastric junction and by type of esophagectomy

		Group		Total	P value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, n (%)	n = 93, n (%)	n = 147, n (%)	
Complications	No	27 (50.0)	60 (64.5)	87 (59.2)	0.084 ¹
	Yes	27 (50.0)	33 (35.5)	60 (40.8)	
Fistulae	No	48 (88.9)	80 (86.0)	128 (87.1)	0.617 ¹
	Yes	6 (11.1)	13 (14.0)	19 (12.9)	
Chylothorax	No	53 (98.1)	93 (100)	146 (99.3)	0.367 ²
	Yes	1 (1.9)	0	1 (0.7)	
Respiratory disorders	No	46 (85.2)	85 (91.4)	131 (89.1)	0.244 ¹
	Yes	8 (14.8)	8 (8.6)	16 (10.9)	
Hoarseness	No	50 (92.6)	93 (100)	143 (97.3)	0.017 ²
	Yes	4 (7.4)	0	4 (2.7)	
Infections	No	50 (92.6)	91 (97.9)	143 (97.3)	0.017 ²
	Yes	4 (7.4)	2 (2.1)	4 (2.7)	
Mortality		2 (3.7)	4 (4.3)	6 (4.08%)	0.342 ²

¹Chi-square test.²Fisher exact test.**Table 3 Number and characteristics of resected lymph nodes of patients with adenocarcinoma of the esophagogastric junction submitted to surgical treatment by transthoracic and transhiatal transthoracic esophagectomy**

		Group		Total	P value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, n (%)	n = 93, n (%)	n = 147, n (%)	
Dissected lymph nodes	mean ± SD	31.89 ± 17.65	20.73 ± 12.70	24.83 ± 15.62	< 0.001 ¹
Metastatic lymph nodes	Median (vmin-vmax)	30 (3-73)	19 (2-85)	22 (2-85)	
	Median (vmin-vmax)	2 (0-25)	1 (0-34)	1 (0-34)	
AL/DL (%)	mean ± SD	15.59 (21.44)	20.56 (28.12)	18.73 (25.90)	0.696 ¹
	Median (vmin-vmax)	5.86 (0-92.31)	5.88 (0-97.14)	5.88 (0-97.14)	

¹Mann-Whitney test. vmin: Minimum; vmax: Maximum; AL/DL: Affected lymph nodes/dissected lymph nodes.

studies suggest fewer pulmonary complications than the transthoracic approach, despite a limited surgical view and difficult mediastinal lymph node resection; it became the preferred access route in AEGJ in Siewert types I and II at our institution for over twenty-five years. After the introduction of minimally invasive surgery with thoroscopic access and standardization of the thoracic lymphadenectomy, and reasonable morbidity results[17], we modified our approach in types I and II AEGJ to transthoracic by thoracoscopy.

It is well-known that post-operative complications after esophagectomy are associated with a worse prognosis[20]. In particular, a higher incidence of respiratory infections (pneumonia and tracheobronchitis) is described in patients undergoing thoracoscopy, due to the fact that there is selective intubation and a longer duration of mechanical ventilation. We also observed this in our series, with respiratory complications occurring in 10.9% of patients in group A.

Table 4 Univariate and multivariate analysis for disease-free survival and overall survival

Disease-free survival	Univariate analysis			Multivariate analysis		
Variables	HR	95%CI	P value	HR	95%CI	P value
Male (<i>vs</i> female)	0.99	0.47–2.08	0.975			
Age (< 62 yr <i>vs</i> > 62 yr)	0.87	0.56–3.14	0.873			
Siewert 1 <i>vs</i> 2	1.11	0.14–8.89	0.921			
TH <i>vs</i> TT (1, 2A)	1.71	1.01–2.90	0.046	1.73	1.00–2.99	0.049
Post-operative complications	1.22	0.56–2.06	0.961			
G3 (<i>vs</i> G1/G2)	1.14	0.61–2.13	0.690			
LN+/LN-	2.61	1.71–3.56	0.001	1.77	0.99–3.24	0.101
pT3/pT4 status (<i>vs</i> pT0/T1/pT2)	2.21	1.86–7.31	0.003	1.56	0.97–3.89	0.102
pN+ (<i>vs</i> pN0)	2.54	1.57–5.78	0.05	1.43	0.88–3.32	0.103
Pathological exam						
Lymphatic	0.78	0.39–1.29	0.783			
Venous	1.67	0.35–2.72	0.246			
Neural	0.78	0.67–1.89	0.183			
Overall survival	Univariate analysis		Multivariate analysis			
Variables	HR	95%CI	P value	HR	95%CI	P value
Age (< 62 yr <i>vs</i> > 62 yr)	0.98	0.89–5.13	0.821			
Siewert 1 <i>vs</i> 2	1.31	0.16–10.68	0.799			
TH <i>vs</i> TT (1, 2A)	2.01	1.19–3.39	0.009	1.79	1.03–3.09	0.038
Post-operative complications	1.03	0.60–1.74	0.927			
G3 (<i>vs</i> G1/G2)	2.37	1.36–4.16	0.003	2.54	1.33–4.82	0.005
LN+/LN-	1.72	1.00–3.48	0.050	1.21	0.87–3.46	0.732
pT3/pT4 status (<i>vs</i> pT0/T1/pT2)	5.95	1.81–19.61	0.003	9.96	2.43–40.74	0.001
pN+ (<i>vs</i> pN0)	1.68	1.38–3.90	0.002	1.18	0.86–4.99	0.735
Pathological exam						
Lymphatic	0.47	0.23–1.78	0.109			
Venous	0.49	0.20–1.06	0.076			
Neural	1.80	0.96–3.35	0.065			

Another complication with an exclusive incidence in group A was hoarseness, probably secondary to mediastinal lymphadenectomy-with consequent manipulation of recurrent laryngeal nerves. In all, four cases were reported in our series. Of these, none evolved with severe speech dysfunction or bronchoaspiration, or the need for a tracheostomy.

The main surgical complication of both surgeries was anastomotic fistula. In this study, it was observed in 12.9% of cases, with no statistical difference between groups. Its prevalence ranges from 15.8% to 30%; although it is accompanied by low morbidity, as anastomosis is located in the neck, with a lower risk of mediastinal infection. When drainage is preferential to the neck incision, it can be managed by endoscopic treatment (3–5 endoscopic dilation sessions)[21].

Regarding surgery-related mortality rate, this study reported 3.7% in the thoracoscopy group and 4.3% in the transhiatal group, with 4.0% overall mortality, showing acceptable results compared to rates up to 15.4% as reported in a systematic review[22].

The number of lymph nodes resected by thoracoscopy was higher (31.89 lymph nodes on average) than transhiatal (20.73 lymph nodes on average), with a significant statistical difference ($P < 0.001$). However, the number of affected nodes were similar.

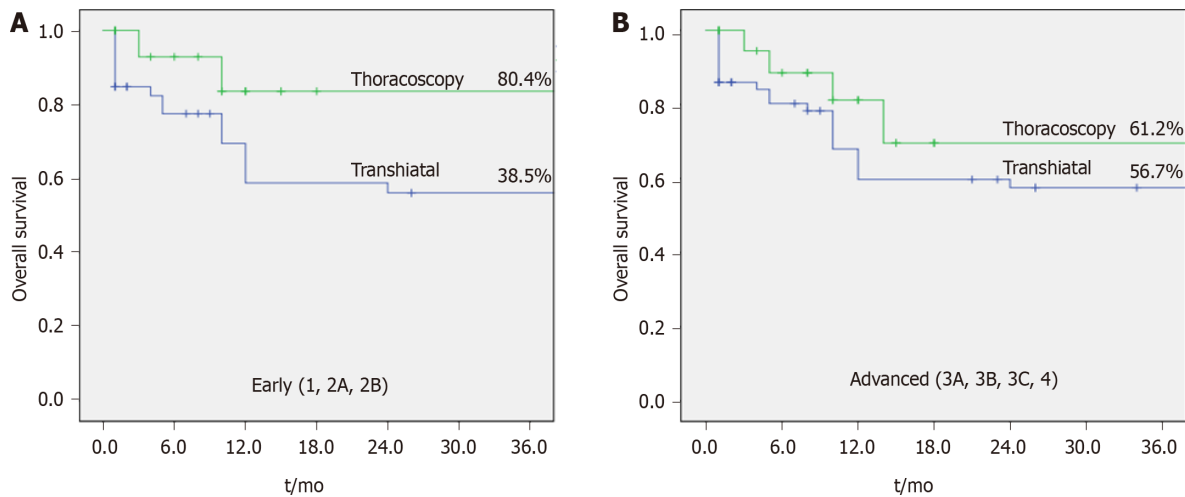


Figure 2 Overall survival of patients with adenocarcinoma of the esophagogastric junction who underwent esophagectomy. A: Early ($P = 0.002$); B: Advanced cases ($P = 0.32$).

With regard to long-term results, what was previously known is that both the transhiatal and transthoracic techniques resulted in similar oncological outcomes, with a tendency for greater perioperative morbidity with the transthoracic pathway[22-24], which is similar to our results.

However, when we analyzed OS and DFS for each clinical stage in isolation, we observed a trend of encouraging results in group A in the earlier stages (up to 2B).

Despite the close follow-up, this study has limitations such as the retrospective design and thus, patients were not randomly selected. There were some disparities in the neoadjuvant treatment between groups (87% in thoracoscopic *vs* 46% in transhiatal) which may be considered a limitation. However, the study aimed to assess overall survival on AEGJ tumors considering a cohort of patients in a “real-world” setting. The neoadjuvant therapy was indicated just in patients > 3A staged. Therefore, neoadjuvant treatment did not interfere in the early stage subgroup analysis. Regarding advanced stages, we believe that the possible limitation related to the difference between groups receiving neoadjuvant chemotherapy was minimized by the multivariate analysis.

CONCLUSION

Both esophagectomy approaches have low morbidity and mortality, given the magnitude of the procedures. Hoarseness and infectious complications were more significant in transthoracic esophagectomy by thoracoscopy. However, it allowed the resection of a more significant number of lymph nodes. In addition, this method is apparently associated with higher OS and DFS at earlier stages and may be a better approach. Further studies are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Extension of lymphadenectomy during esophagectomy is on debate for adenocarcinoma of the esophagogastric junction. Thoracoscopic transthoracic access is considered superior regarding retrieved lymph nodes comparing to transhiatal esophagectomy, but overall survival is questionable.

Research motivation

To understand the relationship between extension of lymphadenectomy and survival according to type of surgical approach.

Research objectives

To compare outcomes after thoracoscopic esophagectomy and transhiatal approach for adenocarcinoma of the esophagogastric junction.

Research methods

Retrospective review of medical records of patients were assessed. A total of 147 patients with adenocarcinoma of the esophagogastric junction were selected from 2002 to 2019, and divided into group A (thoracoscopic esophagectomy), and group B (transhiatal esophagectomy). Overall survival (OS), disease-free survival, post-operative complications, and number of nodes, were similarly evaluated.

Research results

Concerning the extent of lymphadenectomy, group A showed a higher number of retrieved lymph nodes (mean of 31.89 ± 8.2 vs 20.73 ± 7 ; $P < 0.001$), with more perioperative complications, such as hoarseness, surgical site infections, and respiratory complications. Although both groups had similar OS rates, subgroup analysis showed better survival of transthoracic esophagectomy in patients with earlier diseases.

Research conclusions

Both methods are safe, having similar morbidity and mortality rates. Transthoracic thoracoscopic esophagectomy allows a more extensive resection of the lymph nodes and may have better oncological outcomes during earlier stages of the disease.

Research perspectives

Prospective randomized trials addressing topics as long-term survival, the role of neoadjuvant therapies and costs.

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Prospective Study

Prospective evaluation of the hemorrhoid energy treatment for the management of bleeding internal hemorrhoids

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Author contributions: Kothari TH designed and conceptualized the study; Bittner K collected the data; Kothari TH, Bittner K, Kaul V and Kothari S contributed planning/conducting the study (literature review), interpretation of data, drafting/editing the manuscript, and approved the final draft.

Institutional review board

statement: The study was reviewed and approved by the Research Subjects Review Board (University of Rochester Medical Center; approval #780).

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

Conflict-of-interest statement: All authors have no conflict of interest to report.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was

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Abstract

BACKGROUND

The hemorrhoid energy treatment (HET) system is a non-surgical bipolar electrotherapy device, which has previously demonstrated efficacy in the management of bleeding Grade I and II internal hemorrhoids; however, data is limited.

AIM

To prospectively assess the safety and efficacy of the HET device.

METHODS

This was an IRB-approved prospective study of 73 patients with Grade I or II internal hemorrhoids who underwent HET from March 2016 to June 2019. Patient factors and procedural data were obtained. A post-procedure questionnaire was administered by telephone to all patients at 1-wk and 3-mo following HET to assess for improvement and/or resolution of rectal bleeding and adherence to a stool softener regimen. A chart review was performed to observe recurrent symptoms and durability of response. Statistical analyses were performed using SPSS software (IBM; SPSS Version 25.0).

RESULTS

Seventy-three patients underwent HET during the study period. Mean post-HET follow-up was 1.89 years. Complete resolution of bleeding was reported in 65% at 1 wk ($n = 48$), with improvement in bleeding in 97.2% ($n = 71$) of patients. At 3-mo, resolution and/or improvement in bleeding was reported in 90% ($n = 64$) of patients. No procedure-related pain or adverse events were reported.

CONCLUSION

HET is well tolerated, safe and highly effective in the majority of our patients presenting with Grade I and II symptomatic internal hemorrhoids.

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 16, 2020

Peer-review started: December 16, 2020

First decision: March 1, 2021

Revised: April 7, 2021

Accepted: July 19, 2021

Article in press: July 19, 2021

Published online: August 16, 2021

P-Reviewer: Lan C

S-Editor: Gao CC

L-Editor: A

P-Editor: Wang LYT



Key Words: Internal hemorrhoids; Bleeding hemorrhoids; Painless bleeding; Mucus; Constipation; Straining

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Core Tip: Bleeding internal hemorrhoids are a very common problem. More than 50% of population 50 years or older have issues with constipation leading to painless bleeding. Tremendous amount of money is spent in urgent care and emergency department visits for painless bleeding. Not many treatment modalities are available for internal hemorrhoids. Hemorrhoid energy treatment is a bipolar equipment for treatment of internal hemorrhoids grade I and II. Our study has reflected the benefits of this device through our prospective trial.

Citation: Kothari TH, Bittner K, Kothari S, Kaul V. Prospective evaluation of the hemorrhoid energy treatment for the management of bleeding internal hemorrhoids. *World J Gastrointest Endosc* 2021; 13(8): 329-335

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/329.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.329>

INTRODUCTION

Internal hemorrhoids (IH) are a very common cause of lower gastrointestinal bleeding (LGIB) with an estimated prevalence in the United States of 4.4%, accounting for an estimated 3.3 million ambulatory care visits annually[1]. Approximately 40% of patients with hemorrhoids are asymptomatic; however, those presenting with symptoms most often report painless bleeding[2]. Conventionally, Grade I and II bleeding IH have been managed with noninvasive therapies that combine dietary and lifestyle modifications, including increased oral fluid intake, reduction of fat consumption, avoidance of straining during bowel movements, and increased fiber intake[3].

For symptomatic patients, several non-surgical outpatient office-based treatments are currently available including rubber band ligation, infrared coagulation, sclerotherapy, bipolar diathermy, laser photocoagulation, and sclerotherapy[4]. The goal of non-surgical treatment is to decrease vascularity, reduce redundant tissue, and increase hemorrhoidal rectal wall fixation to minimize prolapse[3]. Though success has been demonstrated with the above-mentioned techniques, anorectal pain, recurrent bleeding, and recurrence of hemorrhoids are well-reported adverse events[5, 6].

A novel non-surgical bipolar electrotherapy device, the hemorrhoid energy treatment (HET) System, has previously demonstrated efficacy in the management of bleeding Grade I and II IH[7,8]. We present a prospective study to date evaluating the efficacy and safety of HET.

MATERIALS AND METHODS

This was an IRB-approved prospective cohort study (Research Subjects Review Board, University of Rochester, Study #780) conducted at our tertiary care referral center from 03/2016 to 06/2019. Adult patients (≥ 18 years old) with Grade I or Grade II IH scheduled for outpatient treatment with the HET system during the study period were eligible for inclusion. Written informed consent was obtained prior to study enrollment. All enrolled patients were contacted at 1-week post-procedure to assess improvement in rectal bleeding and self-reported compliance with stool softener use. At 3-mo post-procedure, the same survey was administered by telephone to evaluate if resolution or improvement in rectal bleeding had changed, and if compliance with stool softener use continued. All follow-up questionnaires were administered by telephone by one of the authors (Bittner K) utilizing a standardized script for each call. A concurrent chart review was performed to collect patient demographics, procedural and clinical data. All pre- and post-HET office visits with documented occurrences of

bleeding attributed to IH were recorded. Statistical analyses were performed with SPSS software (IBM, SPSS Version 25.0; Armonk, NY, United States).

HET Techniques

The HET Bipolar System (Medtronic, United States) is a modified anoscope, which incorporates bipolar forceps and includes a separate tissue temperature monitor console (Figure 1). HET was utilized with a commercially available electrosurgical generator (ERBE; Marietta, GA, United States)[9]. Ablation of IH can be achieved with the use of one of three techniques. All HET procedures were performed by two advanced endoscopists (TK, VK), with an average procedure time of less than 15 min.

Medtronic anoscopy technique: This technique includes insertion of the bipolar forceps under LED light provided at the top of the forceps and performing the procedure under direct vision. The superior hemorrhoidal plexus area, approximately 1 cm above the proximal extent of the IH, was grasped with the bipolar forceps. After confirming that the tissue grasped is sufficient (by means of same level approximation of three red lines on bipolar forceps handle), bipolar current was applied with using the recommended electrosurgical generator coagulation settings (effect 1, 5 watts; Figure 2A).

Standard technique: Our “standard technique” included the use of gastroscope inside the bipolar forceps to perform the IH ablation under endoscopic vision (Figure 2B). The concept is to target the superior hemorrhoidal plexus. This method was utilized for the majority of patients in our study ($n = 70/73$).

Modified technique: At our center, we developed a technique called the “modified HET technique” that utilizes use of pediatric biopsy forceps for tissue grasping in addition to the use of the standard endoscope to guide the bipolar forceps. This modified technique facilitates the capture of target rectal tissue when flat and difficult to grasp with the bipolar forceps alone. The pediatric biopsy forceps are used to gently pull the tissue immediately proximal to the IH, which allows the superior hemorrhoidal plexus area to enter the forceps better for optimal treatment (Figure 3).

RESULTS

A total of 73 patients were enrolled during the study period (March 2016 through June 2019). The majority of patients were female (53.4%), with mean age of 50.3 years (Table 1). Mean follow-up duration (post-HET) was 1.89 years. Thirty-six patients (49.3%) presented with Grade I and twenty-six (35.6%) with Grade II IH. Grade of IH was not available for 10/73 (13.7%) patients. In one patient, a Grade III hemorrhoid confirmed on colonoscopy immediately prior to treatment. Approximately half of patients (45.2%) failed conservative therapy prior to HET (defined as: stool softeners, fiber supplements and/or hydrocortisone suppositories). Most patients (90.4%) reported persistent painless rectal bleeding at the office visit immediately prior to referral for HET.

HET was performed with flexible sigmoidoscopy in all cases, using a standard gastroscope. Our “standard HET technique” was utilized in 70/73 patients. Three patients were treated with the “modified HET technique”. All patients were contacted by telephone at 1-wk and 3-mo post-procedure (Tables 2 and 3) to complete a questionnaire regarding resolution and/or improvement of bleeding symptoms, and compliance with stool softener use. All patients successfully completed the 1-wk questionnaire; however, 2 patients were unable to be contacted at 3-mo (response rate = 100% and 97.3%, respectively). At 1-wk post-procedure, complete resolution of bleeding was reported in 66% of patients ($n = 48/73$), with improvement in bleeding reported in 97.2% ($n = 71/73$) patients. Polyethylene glycol and/or other stool softeners were prescribed post-procedure to prevent constipation; however, at 3-mo post-HET, only 55% of patients reported continued use.

A concurrent chart review was performed to assess for recurrence or persistence of symptoms and durability of response. At 3-mo post-procedure, complete resolution of bleeding was reported in 62% of patients ($n = 44/71$), with improvement in bleeding reported in 90.1% ($n = 64/71$) patients. Six patients required a repeat HET (mean of 7.6 mo following initial treatment) for persistent rectal bleeding, with complete resolution reported after the 2nd treatment in 3/6 of these patients. Three patients continued to report persistent rectal bleeding despite repeat HET.

Table 1 Patient characteristics

Patient characteristics	n = 73
Age at HET (yr), mean	50.3
Female, n (%)	39 (53.4)
Race, n (%)	
Caucasian	58 (79.5)
African-American	14 (19.2)
Asian	1 (1.4)
Grade of hemorrhoids at time of HET, n (%)	
Grade I	36 (49.3)
Grade II	26 (35.6)
Grade III	1 (1.4)
Not reported	10 (13.7)

HET: Hemorrhoid energy treatment.

Table 2 Responses to telephonic questionnaire

Responses to telephonic questionnaire, 1 wk post-procedure (n = 73)					
Bleeding resolved		Bleeding improved		Use of stool softeners (post-HET)	
Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)
48 (65.8)	25 (34.2)	23 (92.0)	2 (8.0)	36 (49.3)	37 (50.7)

HET: Hemorrhoid energy treatment.

Table 3 Responses to telephonic questionnaire

Responses to telephonic questionnaire, 3 mo post-procedure (n = 71)					
Bleeding resolved ¹		Bleeding ¹ improved		Use of stool softeners (post-HET)	
Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)
44 (62.0)	27 (38.0)	20 (74.1)	7 (25.9)	39 (54.9)	32 (45.1)

¹A total of 64/71 (90.1%) patients reported complete resolution or improvement of bleeding post-hemorrhoid energy treatment.

HET: Hemorrhoid energy treatment.

There were no instances of pain or rectal discomfort during or immediately following the HET procedure. One patient reported self-limited post-procedure bleeding. No other adverse events were noted from the procedure.

DISCUSSION

IH are common and can be symptomatic with rectal bleeding in many patients. They are often difficult to treat and can lead to significant morbidity, affect quality of life of the patient and put a significant burden on healthcare. Several non-surgical treatment modalities are available for treatment of Grade I and II bleeding IH. Current treatment guidelines recommend outpatient office-based procedures such as rubber-band ligation (RBL), sclerotherapy or infrared coagulation for patients who remain symptomatic after lifestyle modifications have failed[10].

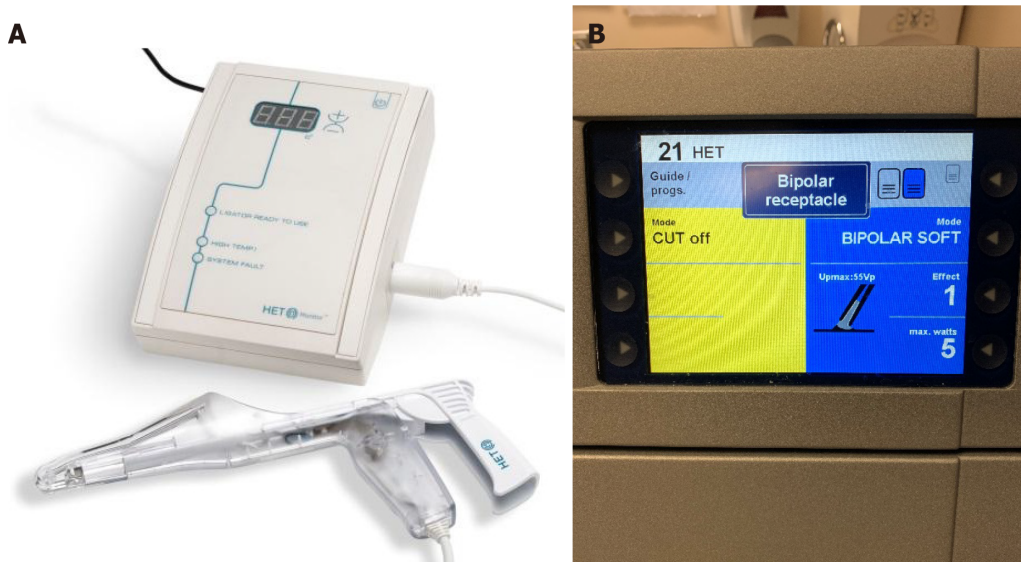


Figure 1 The hemorrhoid energy treatment bipolar system. A: Hemorrhoid energy treatment (HET) system with bipolar forceps and tissue temperature monitor. Permission for use of image granted by HET System, LLC; B: Electro-surgical generator with HET settings.

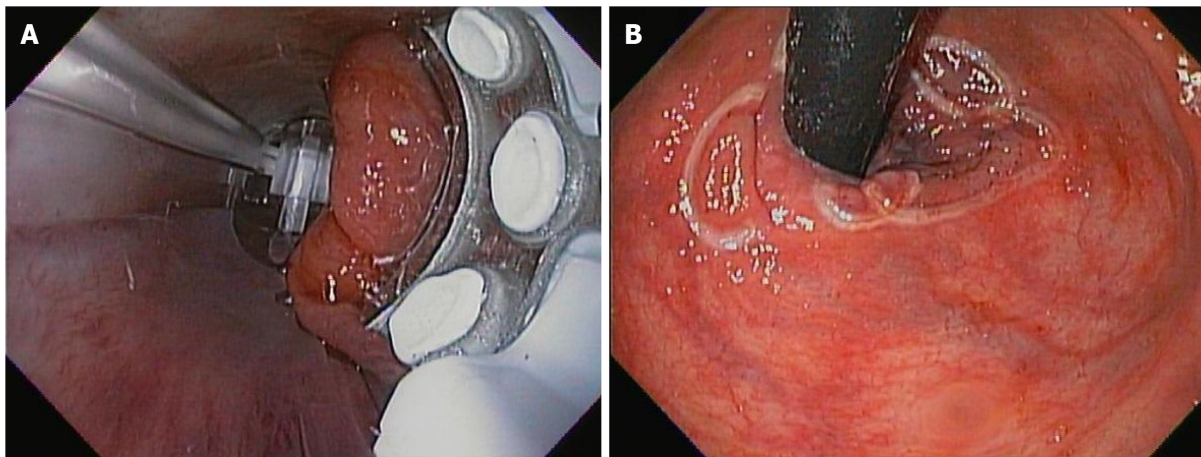


Figure 2 Antegrade view of internal hemorrhoids and retroflexed view of the anal verge. A: Antegrade view of internal hemorrhoids with a standard gastroscope; B: Retroflexed view of the anal verge post hemorrhoid energy treatment suggestive of treatment of multiple internal hemorrhoidal columns.

Rubber band ligation is the most frequently used procedure for hemorrhoid treatment. In a meta-analysis of 18 randomized controlled trials, RBL was noted to have a lower need for repeat treatments compared to sclerotherapy and infrared coagulation, although did cause significantly more pain reported in 25%-50% of patients[11-13].

Sclerotherapy is one of the oldest non-surgical therapy and involves injecting a sclerosant into the submucosa at the base of the hemorrhoid. Due to the nature of the procedure, there have been adverse events reported such as rectal fistulas and life-threatening retroperitoneal sepsis[14]. In a meta-analysis of randomized controlled studies comparing RBL, sclerotherapy and surgery, sclerotherapy was less effective than rubber band ligation and surgery. Infrared coagulation is less effective than banding or sclerotherapy and requires repeat treatment sessions[11].

HET is a novel non-surgical treatment for IH and has been reported to be both safe and effective in prior studies[7-9]. These studies have had limitations due to the retrospective nature of the study and small sample size. Piskun and Tucker[9] performed a direct comparison of the HET system with infrared coagulation in a live porcine model with favorable outcomes. The HET device combined target tissue compression with precise application of much lower temperature (55 °C) *vs* that of the infrared coagulation probe (149 ± 11.1 °C), minimizing heat-related collateral damage to tissues adjacent to the treatment areas. The authors concluded that the treatment with the HET System would cause less procedural pain and less post-procedural

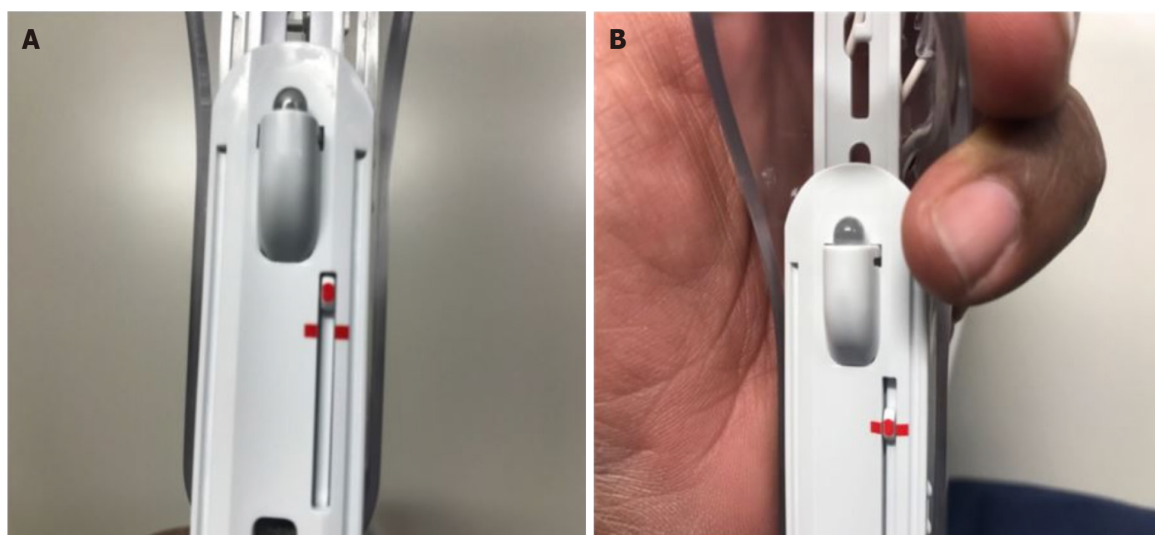


Figure 3 The pediatric biopsy forceps. A and B: Sufficient entrapment of the mucosa above the internal hemorrhoids is indicated with alignment of all three red lines.

adverse events *vs* existing non-surgical modalities for treatment of IH[9]. In 2013, Kantsevov and Bitner[8] conducted a retrospective study of examining the use of HET for the indication of actively bleeding IH. All patients in this cohort ($n = 23$) tolerated the treatment without any pain or discomfort. No adverse events were reported in the study[8]. In 2016, Crawshaw *et al*[7] reported the safety and efficacy of HET technology in a prospective case series of 20 patients with bleeding improvement seen in $> 80\%$ of the patients.

Our study demonstrates the safety and efficacy of the HET platform in the treatment of Grade I and Grade II IH. Nearly half of patients had failed guideline-based conservative therapy prior to referral for HET. The majority of our cohort reported no immediate post-procedural pain or bleeding. Complete resolution and/or improvement in bleeding symptoms were reported in 97.2% and 90.1 % of patients at 1-week and 3-months post-procedure, respectively.

The main limitations of this study were relatively small sample size ($n = 73$), lack of comparison or control arm, and is our single-center's experience with HET use. The potential for lack of generalizability may exist due to the level of expertise of the endoscopists performing the HET procedure at our institution.

CONCLUSION

Our study represents one of the largest prospective studies reporting safety and efficacy for the use of HET system in patients with symptomatic Grade I and II IH. Further multi-center prospective studies are needed to validate the efficacy and safety of the device. In addition, these studies should also assess if the use of stool softeners for a brief period post-HET prevents recurrence of rectal bleeding.

ARTICLE HIGHLIGHTS

Research background

Painless rectal bleeding (*i.e.*, Grade I and Grade II Internal hemorrhoids) can be effectively treated with hemorrhoid energy treatment (HET). Our study has demonstrated that the procedure is safe, well tolerated and clinically effective for most patients.

Research motivation

There has been limited treatment for internal hemorrhoids, hence this manuscript is intended to add real-world clinical data to the literature.

Research objectives

To educate readers with clinical data regarding treatment of bleeding internal hemorrhoids with the help of HET system.

Research methods

This research study was a prospective cohort design.

Research results

The majority of patients reported complete resolution and/or improvement in bleeding resulting from internal hemorrhoids at 3-mo post-procedure.

Research conclusions

HET system can make a significant impact in treatment of bleeding internal hemorrhoids.

Research perspectives

Further research should be performed to expand upon our findings.

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Effect of pancreatic endotherapy on quality of life in chronic pancreatitis patients: A systematic review

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Author contributions: Han SY and Conwell DL wrote the paper; Papachristou GI and Shah RJ reviewed and revised the paper.

Conflict-of-interest statement: Papachristou GI is a Consultant for Olympus, and has received research funding from AbbVie; Author Shah RJ is an Advisory Board Member and Consultant for Boston Scientific and Consultant for Olympus and Cook Endoscopy; Conwell DC received support from the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number U01 DK108327.

PRISMA 2009 Checklist statement: This manuscript was presented in accordance with the PRISMA guidelines for a systematic review.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

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Abstract

BACKGROUND

Pancreatic endotherapy provides treatment options for the management of chronic pancreatitis-related structural complications such as pancreatic duct stones, strictures, and pancreatic fluid collections. Most studies detailing endotherapy, however, have focused on technical success outcomes such as stone clearance or stricture resolution.

AIM

To review the effect of pancreatic endotherapy on patient-centered outcomes.

METHODS

Systematic review of studies examining pancreatic endotherapy.

RESULTS

A total of 13 studies including 3 randomized clinical trials were included. The majority of studies found an improvement in quality of life with pancreatic endotherapy.

CONCLUSION

While pancreatic endotherapy does appear to improve quality of life, there are clear gaps in knowledge regarding many pancreatic endotherapy modalities. Furthermore, qualitative analysis is lacking in these studies and further work is needed to elucidate the patient experience with pancreatic endotherapy.

Key Words: Chronic pancreatitis; Pancreatic endotherapy; Endoscopic retrograde cholangiopancreatography; Quality of life

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 2
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 12, 2021

Peer-review started: February 12, 2021

First decision: May 5, 2021

Revised: June 11, 2021

Accepted: July 13, 2021

Article in press: July 13, 2021

Published online: August 16, 2021

P-Reviewer: Dedemadi G

S-Editor: Zhang H

L-Editor: A

P-Editor: Xing YX



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Core Tip: Chronic pancreatitis remains difficult to treat and pancreatic endotherapy offers one option for the management of chronic pancreatitis-related complications. Pancreatic duct decompression *via* pancreatic duct stone lithotripsy and stenting appears to improve the quality of life of these patients in the short-term. More studies, however, are needed to examine the effect of endotherapy modalities such as endoscopic transmural drainage of pancreatic fluid collections, celiac plexus blocks and more recent innovations on quality of life in these patients.

Citation: Han SY, Papachristou GI, Shah RJ, Conwell DL. Effect of pancreatic endotherapy on quality of life in chronic pancreatitis patients: A systematic review. *World J Gastrointest Endosc* 2021; 13(8): 336-355

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/336.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.336>

INTRODUCTION

Pain, the hallmark feature of chronic pancreatitis (CP), remains difficult to manage effectively and can significantly worsen patients' quality of life[1-3]. A variety of factors likely play a role in the mechanism of pain, which can include ductal hypertension, inflammation, or neuropathic pain from varying degrees of sensitization of the nervous system[1,4]. Targeted treatment based on the etiology of the pain therefore is challenging and initial treatment will typically consist of medical management.

Pancreatic endotherapy (PET) offers a treatment option for patients with CP-related structural complications such as pancreatic duct (PD) stones, strictures, stones, or pancreatic fluid collections such as pseudocysts. Patients must typically fail medical management before PET is considered with persistent pain being the most common indication. The last decade has ushered in a wave of new PET modalities that have advanced the field beyond standard endoscopic retrograde pancreatography. For PD stones, per-oral pancreatoscopy (POP)-guided lithotripsy using electrohydraulic lithotripsy or laser lithotripsy have dramatically increased the rates of successful PD stone clearance[5,6]. For pancreatic duct strictures, the use of fully covered metal stents, wire-guided cystotomes, and POP-guided laser dissection have greatly expanded the armament of the endoscopist for these refractory stenoses[7-11]. Lastly, the development of lumen-apposing metal stents has revolutionized the drainage of pancreatic fluid collections by facilitating endoscopic transmural drainage in a single step[12,13].

Despite these advances in PET, published studies have largely focused on technical success outcomes such as stricture resolution or stone clearance[5,6,14-16]. Furthermore, the few randomized studies have centered on pain improvement as the primary outcome, which while important, does not capture the holistic impact of PET on patients. As patients and physicians will have different priorities, expectations, and preferences regarding treatment choices, it is critically important to incorporate patient-centered outcomes such as quality of life in the evaluation of these modalities [17]. Therefore, the aim of this review is to detail the effect of PET on quality of life in patients with CP.

MATERIALS AND METHODS

Literature search strategy

We searched PubMed for relevant English-language articles published by January 5, 2021 with no restriction on earliest publication date. The search terms included quality of life and each of the following: endoscopic therapy, endoscopic retrograde cholangiopancreatography (ERCP), celiac plexus block, pancreatic duct stone, pancreatic duct stricture, pancreatic duct stent, pancreatic fluid collection, pseudocyst, pancreatoscopy, lithotripsy, and endoscopic ultrasound.

Inclusion and exclusion criteria

The relevance of the studies was determined using the hierarchical approach as recommended by the PRISMA statement. We assessed the studies by examining the title, abstract, and/or full text of the studies. We also examined the references of included studies to identify any additional studies. Inclusion criteria included the following: (1) Studies involving PET that included quality of life as an outcome; (2) Publication in the English language; (3) Availability of the full text; and (4) Publication date by January 5th, 2021. Exclusion criteria included the following: (1) Non-original studies including reviews, editorials, commentaries, and study protocols; (2) Insufficient data; and (3) Duplicate studies (*i.e.*, conference abstract and full-text manuscript).

RESULTS

The literature search flow diagram is presented in [Figure 1](#). The initial PubMed database search yielded a total of 10, 242 articles. Upon title and abstract review, the full text of 123 articles were reviewed. Upon excluding 110 of these studies, which were found to be irrelevant, a total of 13 studies, including 3 randomized clinical trials and 10 observational studies were included ([Table 1](#)).

Comparison of surgery with endoscopy for pancreatic duct drainage

The major randomized trials comparing endoscopy with surgery focus on pancreatic duct drainage to relieve ductal hypertension. In the landmark trial comparing endoscopic treatment [ERCP with stricture dilation for PD strictures \pm extracorporeal shock-wave lithotripsy (ESWL) for concomitant PD stones] with a side-to-side pancreaticojejunostomy, at 2 year follow-up patients who received endotherapy ($n = 19$) had an improvement in both physical health (31 ± 8 to 38 ± 9) and mental health (33 ± 8 to 40 ± 9) on the 36-Item Short Form Health Survey (SF-36) questionnaire[18]. While this was less than the improvement in quality of life seen in the surgery arm, in the follow-up study examining long-term (mean follow-up of 79 mo) outcomes of both arms, the improvement in both physical and mental quality of life persisted, but there was no longer any difference between the two arms[19]. More recently, the ESCAPE trial from the Dutch pancreatitis study group randomized patients with painful CP and a dilated PD to either early pancreatic drainage surgery ($n = 44$) or endotherapy (ERCP \pm ESWL) first ($n = 44$)[20]. At 18 mo follow-up, patients in the endotherapy arm did experience an improvement in both physical (31 ± 8 to 36 ± 9) and mental (36 ± 11 to 41 ± 11) health on the SF-36 with no difference seen in quality of life between the two treatment groups. Lastly, in a retrospective study comparing surgery with endotherapy, the European Organization for Research and Treatment of Cancer (EORTC) quality of life instrument and the pancreatic cancer module (PAN26) instrument were utilized with the primary finding that patients treated with surgery had less nausea and vomiting [21].

Pancreatic duct stone therapy

Internationally, the combination of ESWL with ERCP represents the most common form of treatment for symptomatic PD stones. Starting with a prospective study by Brand *et al*[22] in 2000, ESWL followed by ERCP was associated with an improvement in pain, weight loss, fevers/chills, jaundice, and global quality of life on the EORTC instrument. Within an Indian patient population, Tandan *et al*[23] presented a large study ($n = 636$) of this treatment modality, finding that using a scale of 1-10 (10 representing the best quality of life), quality of life improvement was seen in 92.8% of patients at 2-5 year follow-up and in 92.6% of patients at > 5 year follow-up. In a large Chinese patient cohort using the SF-36, a significant improvement was seen in overall quality of life and physical health, but not in mental health[24,25]. Seven *et al*[26] presented data on this PET combination in a United States cohort, utilizing a 1-10 quality of life score (10 being the best quality of life), finding a significant improvement in quality of life (3.7 ± 2.4 to 7.3 ± 2.7) after completion of therapy. Similarly, in a study from Germany, Milovic *et al*[27] reported a significant improvement in quality of life after ESWL and ERCP on a 5-point quality of life scale (2.5 to 4).

In the only study examining pancreatoscopy-guided lithotripsy that included quality of life as a study outcome, Gerges *et al*[28] utilized both electrohydraulic and laser lithotripsy in 20 patients. They found that post-therapy, 89% of patients had no or only mild disability in daily activities and 47% of patients described their health as

Table 1 Key characteristics of included articles

Ref.	Study design	Endoscopic modality	n	Quality of life measurement	Quality of life findings
Cahen <i>et al</i> [18,19]	Randomized clinical trial	ERCP ± ESWL	19	SF-36	Physical health: 31 ± 8 to 38 ± 9 (2 yr) and 43 ± 11 (7 yr); Mental health: 33 ± 8 to 40 ± 9 (2 yr) and 46 ± 9 (7 yr)
Issa <i>et al</i> [20]	Randomized clinical trial	ERCP ± ESWL	44	SF-36	Physical health: 31 ± 8 to 36 ± 9; Mental health: 36 ± 11 to 41 ± 11
Stevens <i>et al</i> [31]	Randomized study	Celiac plexus block	40	SF-12	Change in physical score: -0.2 ± 7.5 (triamcinolone + bupivacaine), 1.7 ± 8.8 (bupivacaine); Change in mental score: 1.3 ± 10.0 (triamcinolone + bupivacaine), -2.1 ± 12.9 (bupivacaine)
Brand <i>et al</i> [22]	Prospective study	ERCP + ESWL	48	EORTC	Pain: 37.8 (range 0-81.5) to 18.8 (range 0-83.3); Weight loss: 66.7 (range 0-100) to 0 (range 0-100); Global quality of life: 41.7 (range 16.7-100) to 58.3 (range 8.3-100)
Hu <i>et al</i> [24]	Prospective study	ERCP + ESWL	214	SF-36	Physical health: 56.9 ± 18.7 to 59.2 ± 14.8 (no significant difference); Patients with pseudocysts: 95 (range 35-100) to 100 (range 75-100); Mental health: 52.2 ± 21.5 to 58.5 ± 16.4; Patients with pseudocysts: 68 (range 36-100) to 76 (range 28-100)
Milovic <i>et al</i> [27]	Prospective study	ERCP + ESWL	32	1-5 scale	4 (range 2-5) to 2.5 (range 1-4)
Basiński <i>et al</i> [32]	Prospective study	Celiac plexus block	92	EORTC	Quality of life significantly improved with greatest improvement seen in those with high religiosity
Rutter <i>et al</i> [21]	Retrospective study	ERCP	150	EORTC	Patients treated with surgery had less nausea/vomiting compared to those treated with endoscopy
Tandan <i>et al</i> [23]	Retrospective study	ERCP + ESWL	636	1-10 scale	252 (92.6%) patients had improved quality of life
Seven <i>et al</i> [26]	Retrospective study	ERCP + ESWL	120	1-10 scale	3.7 ± 2.4 to 7.3 ± 2.7
Gerges <i>et al</i> [28]	Retrospective study	Pancreatotomy-guided lithotripsy	20	Generic quality of life instrument	89% had no or only mild disability in daily activities, 47% had “excellent” or “very good” general health
Vitale <i>et al</i> [29]	Retrospective study	Minor papilla stenting	32	Generic quality of life survey	100% stated improved quality of life, 100% stated satisfaction with treatment

ERCP: Endoscopic retrograde cholangiopancreatography; ESWL: Extracorporeal shock-wave lithotripsy; SF: Short Form Health Survey; EORTC: European Organisation for Research and Treatment of Cancer.

“excellent” or “very good.”

Minor papilla endotherapy

Minor papilla endotherapy typically involves performing a minor papilla sphincterotomy and/or stenting. Depending on the presence of strictures or stones, endotherapy can also include dilation or stone lithotripsy. A single-center study examining 32 patients with CP and pancreas divisum-related strictures assessed quality of life through telephone surveys asking about their overall quality of life and their level of satisfaction post-treatment[29]. All subjects treated *via* endotherapy reported improved quality of life and satisfaction in their treatment.

Pancreatic fluid collection drainage

There were no studies examining transmural drainage of CP-associated pancreatic fluid collections that included quality of life as an outcome. In regards to patients with acute necrotizing pancreatitis, however, Smith *et al*[30] performed a single-center cross-sectional study examining patients treated with endoscopic ultrasound-guided transmural drainage of walled-off necrosis. Using the SF-36, the authors found that at 2 year follow-up, patients treated with transmural drainage had equivalent scores to a healthy control population in nearly all domains with the exception of the physical role and general health domains, where they had significantly lower scores (physical role: 58.5 ± 40.9 *vs* 81.0 ± 34.0, general health: 56.9 ± 25.8 *vs* 72.0 ± 20.3). Notably, these subjects had significantly higher quality of life scores in domains such as pain and vitality compared to patients with irritable bowel syndrome.

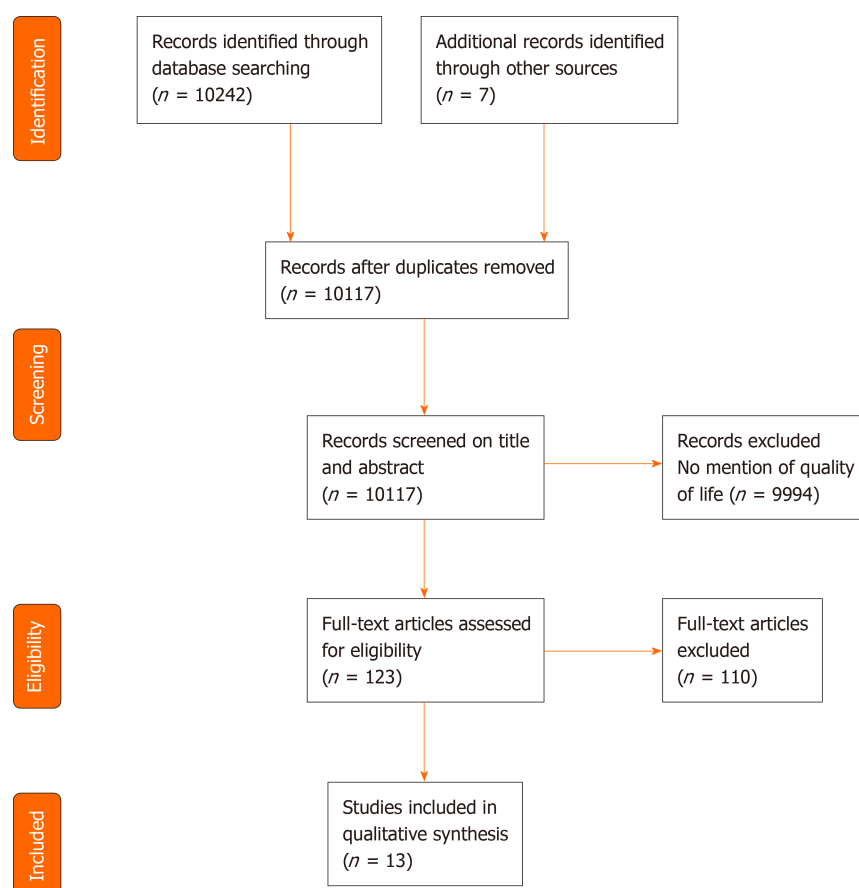


Figure 1 PRISMA flow diagram of article selection.

Celiac plexus block

In a single-center randomized study comparing celiac plexus block (using bupivacaine) with and without triamcinolone for patients with painful CP, pre and post-therapy quality of life was assessed using the SF-12[31]. The study was stopped prematurely at interim analysis due to no difference between the two treatment arms in improving pain and no significant differences in physical and mental quality of life were seen between the 2 arms. The triamcinolone arm saw a change of -0.2 ± 7.5 for physical health and a change of 1.3 ± 10.0 in mental health while the control arm saw a change of 1.7 ± 8.8 in physical health and a change of -2.1 ± 12.9 in mental health. In a study from Poland, Basiński *et al*[32] utilized the EORTC quality of life questionnaire, finding improvement in quality of life at 1- and 4-wk follow-up. Stratifying patients on their level of religiosity, the greatest improvement in quality of life was seen in those with high religiosity at both time points.

DISCUSSION

In this systematic review, while we demonstrate that PET does appear to improve quality of life in patients with CP, the most striking finding is the overall lack of evidence in many of these PET modalities. The majority of evidence comes from endoscopic treatment of pancreatic ductal obstruction secondary to PD stones and strictures with the 2 Landmark trials by Cahen *et al*[18] and Issa *et al*[20] comparing surgical with endoscopic drainage. There remain clear gaps in knowledge regarding how endoscopic therapies such as celiac plexus block, pancreatoscopy-guided therapies, endoscopic transmural drainage of pancreatic fluid collections and minor papilla endotherapy affect quality of life in the CP population. This highlights the continued emphasis of endoscopic studies on technical success outcomes rather than patient-centered outcomes and while PET modalities will continue to expand, without understanding the impact of these therapies on patients, choosing the best treatment for each individual patient becomes even more challenging.

As shown in Table 1, studies most often measured quality of life using the SF-36 and the EORTC quality of life instrument, which while validated, are not disease-specific for chronic pancreatitis. The remaining studies assessed quality of life by simply asking about quality of life, speaking to need for more rigorous research in quality of life within this field of endotherapy. The PANcreatitis Quality of Life Instrument is a validated chronic pancreatitis-specific quality of life instrument consisting of 18 items that includes sub-scores for physical function, role function, emotional function, and self-worth domains[33]. Additionally, the National Institute of Health has developed the Patient-Reported Outcomes Measurement Information System instruments to standardize measurement of patient-reported outcomes such as quality of life and pain. Incorporating instruments such as these can facilitate future research in this arena by capturing critical quality of life aspects pertinent to this patient population.

Pain remains the center point of quality of life in patients with CP as constant pain and severe pain, in particular, are associated with worse quality of life[2,34]. Similar to quality of life, pain has been poorly measured in prior PET studies with most reporting a visual analog scale score or the Izicki pain score, which are simplified assessments of pain[35]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials has recently called for improved phenotyping of pain in an effort to deliver the most appropriate therapy based on an individual patient's pain characteristics[36]. In line with this, pancreatic quantitative sensory testing (QST) represents a novel method of characterizing sensory processing in the peripheral and central pain pathways[37]. While data has demonstrated how QST can be used to predict the efficacy of pregabalin in CP patients, much work is needed to determine if QST can help predict *a priori* which patients will respond to PET[38]. Nevertheless, there remains much promise in using tools such as QST to better characterize pain profiles in patients with CP to ultimately develop an algorithm-based approach to the management of this challenging disease.

In addition to the quantitative analysis done in these studies, qualitative studies are needed to truly encapsulate subjects' experiences with PET and better understand how PET affects their disease. Quantitative assessment of quality of life captures only a portion of the patient's overall well-being and given the lack of qualitative studies centered around endotherapy, future endeavors are certainly needed to incorporate the patient's perspective. Understanding factors such as patient expectations, regret, suffering, and coping may help design future randomized sham-controlled trials with patient-centered outcomes to help determine which PET modalities are most effective in which patients.

CONCLUSION

In summary, given the dearth of treatment options for CP, PET offers a viable therapy for patients with CP-related complications such as PD stones and strictures. Much work is needed, however, to elucidate the patient experience with PET and identify who will respond to PET with the ultimate goal of providing individualized treatment plans for these patients.

ARTICLE HIGHLIGHTS

Research background

While pancreatic endotherapy is frequently performed for the treatment of chronic pancreatitis-related complications, most studies examining endotherapy have focused on technical success outcomes, such as stricture resolution or stone clearance. Studies reporting patient-centered outcomes such as quality of life are lacking, however, making it difficult to determine how endotherapy affects these patients.

Research motivation

The motivation for this systematic review stems from the primary criticism of pancreatic endotherapy on whether endotherapy improves the lives of patients with chronic pancreatitis. While it is well-known that endotherapy can treat the structural complications of chronic pancreatitis, the effect of endotherapy on patient-centered outcomes is poorly studied.

Research objectives

The primary objective of this systematic review was to detail the literature regarding how pancreatic endotherapy affects quality of life in chronic pancreatitis patients.

Research methods

A systematic review was performed to identify studies reporting on various pancreatic endotherapy modalities and quality of life.

Research results

The search yielded 13 studies for review out of 10242 articles. All of the modalities examined found an improvement in quality of life.

Research conclusions

Pancreatic endotherapy does appear to improve quality of life, but the assessment of quality of life is very heterogeneous and not disease-specific. Furthermore, there is a lack of evidence regarding many modalities such as transmural fluid drainage, pancreatoscopy-guided therapy and celiac plexus block.

Research perspectives

Further studies are clearly needed to elucidate the patient experience with receiving pancreatic endotherapy and future trials will benefit from having patient-centered outcomes as the primary outcome.

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Efficacy and safety of endoscopic transpapillary gallbladder drainage in acute cholecystitis: An updated meta-analysis

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Author contributions: Jandura DM contributed to the design, analysis, and interpretation of the data, writing of the article, and critical revision of the article; Puli SR contributed to the conception, analysis, and final approval of the article.

Conflict-of-interest statement: The authors declare no conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Percutaneous transhepatic gallbladder drainage has been the most frequently performed treatment for acute cholecystitis for patients who are not candidates for surgery. Endoscopic transpapillary gallbladder drainage (ETGBD) has evolved into an alternative treatment. There have been numerous retrospective and prospective studies evaluating ETGBD for acute cholecystitis, though results have been variable.

AIM

To evaluate the efficacy and safety of ETGBD in the treatment of inoperable patients with acute cholecystitis.

METHODS

We performed a systematic review of major literature databases including PubMed, OVID, Science Direct, Google Scholar (from inception to March 2021) to identify studies reporting technical and clinical success, and post procedure adverse events in ETGBD. Weighted pooled rates were then calculated using fixed effects models for technical and clinical success, and post procedure adverse events, including recurrent cholecystitis.

RESULTS

We found 21 relevant articles that were then included in the study. In all 1307 patients were identified. The pooled technical success rate was 82.62% [95% confidence interval (CI): 80.63-84.52]. The pooled clinical success rate was found to be 94.87% (95%CI: 93.54-96.05). The pooled overall complication rate was 8.83% (95%CI: 7.42-10.34). Pooled rates of post procedure adverse events were bleeding 1.03% (95%CI: 0.58-1.62), perforation 0.78% (95%CI: 0.39-1.29), peritonitis/bile leak 0.45% (95%CI: 0.17-0.87), and pancreatitis 1.98% (95%CI: 1.33-2.76). The

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Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 23, 2021

Peer-review started: April 23, 2021

First decision: June 7, 2021

Revised: June 21, 2021

Accepted: July 5, 2021

Article in press: July 5, 2021

Published online: August 16, 2021

P-Reviewer: Martínez-Pérez A, Sekine K

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Li JH



pooled rates of stent occlusion and migration were 0.39% (95%CI: 0.13-0.78) and 1.3% (95%CI: 0.75-1.99) respectively. The pooled rate of cholecystitis recurrence following ETGBD was 1.48% (95%CI: 0.92-2.16).

CONCLUSION

Our meta-analysis suggests that ETGBD is a feasible and efficacious treatment for inoperable patients with acute cholecystitis.

Key Words: Endoscopic transpapillary gallbladder drainage; Acute cholecystitis; Inoperable treatment; Double pigtail stent; Nasobiliary drainage

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Core Tip: We offer the most updated meta-analysis evaluating the efficacy, feasibility and safety of endoscopic transpapillary gallbladder drainage for the treatment of inoperable acute cholecystitis. We included 21 studies in our analysis. Our results conclude that this modality of gallbladder drainage is safe and efficacious.

Citation: Jandura DM, Puli SR. Efficacy and safety of endoscopic transpapillary gallbladder drainage in acute cholecystitis: An updated meta-analysis. *World J Gastrointest Endosc* 2021; 13(8): 345-355

URL: <https://www.wjgnet.com/1948-5190/full/v13/i8/345.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v13.i8.345>

INTRODUCTION

Cholelithiasis is a common condition that affects 6% of men and 9% of women in the United States[1]. Acute cholecystitis is a syndrome of right upper quadrant abdominal pain, fevers and leukocytosis that is associated with inflammation of the gallbladder. Occurring in about 6%-11% of patients with symptomatic gallstones, it is the most common gallbladder syndrome[2]. The standard of care treatment for acute cholecystitis is antibiotic therapy and definitive surgical intervention with cholecystectomy. For patients unsuitable for surgery, the ideal choice has been percutaneous transhepatic drainage.

Percutaneous drainage is well established in the literature with strong technical success rates of nearly 97%, and with more variable clinical response rates ranging from 56%-100%[3-5]. Though effective, complications related to externalized drainage including bile leakage, peritonitis, bleeding and catheter misplacement/removal have been noted[6]. Patient satisfaction and quality of life have also been of concern, with patient discomfort occurring in up to 25% of patients[7]. Coagulopathy and decompensated liver disease with ascites have also been contraindications to percutaneous drainage[8,9]. Another drawback to percutaneous drainage is that it may be an impermanent solution. Patients who did not undergo cholecystectomy following percutaneous catheter removal had significant recurrence rates of cholecystitis ranging from 22%-47%[10,11].

Endoscopic techniques for gallbladder drainage have been evaluated in inoperable patients with cholecystitis who are not suitable for percutaneous drainage. Two endoscopic approaches to gallbladder drainage exist, they include a transmural approach performed with endoscopic ultrasound (EUS), and endoscopic transpapillary gallbladder drainage (ETGBD) which utilizes endoscopic retrograde cholangiopancreatography (ERCP). EUS guided gallbladder drainage was first described in 2007, with well-established efficacy. Technical and clinical success rates of 84.6%-100% and 86.7%-100% respectively have been demonstrated[12,13]. Drawbacks, such as the need for a high level of expertise, procedure costs and the risk of adverse events in the setting of technical failure, have been noted. The development of lumen opposing stents (LAMS) has improved the feasibility and efficacy and has helped to decrease the rate of procedure related complications. Nevertheless, there is uncertainty of the effects of retained LAMS and its contribution to adverse events as well as its effect on future surgical options.

Transpapillary gallbladder drainage is an important option for inoperable patients requiring treatment of acute cholecystitis. It consists of ERCP bile duct cannulation followed by endoscopic transpapillary gallbladder stenting or endoscopic nasobiliary gallbladder drainage (ENGBD). Both approaches have been useful in patients with concomitant choledocholithiasis or in the presence of biliary stricture. Unlike ENGBD, a transpapillary approach has evolved as an especially advantageous method due to its relatively non-invasive nature with improved patient quality of life without the need for externalized drainage. Drawbacks to this method include the potential for post ERCP complications, along with the technical difficulty of the procedure itself, though there have been variable results in the literature. We performed a systematic review including more recent studies evaluating ETGBD in inoperable patients with acute cholecystitis. We present an updated meta-analysis evaluating the technical and clinical success of ETGBD. We also evaluate the safety of ETGBD by analyzing pooled rates of procedural adverse events.

MATERIALS AND METHODS

Search methodology

We performed a literature search using the electronic database engines PubMed, OVID, ScienceDirect, Google scholar from inception to March 2021 to identify published articles and reports which addressed the use of ETGBD as treatment for acute cholecystitis. The search terms “endoscopic transpapillary gallbladder drainage”, “acute cholecystitis”, “complications”, “technical success”, “clinical success”, “adverse events” in different combinations were used. The reference lists of eligible studies were reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Resultant titles and abstracts were selected from the initial search, they were scanned, and the full papers of potential eligible studies were reviewed.

Study eligibility

The relevance of the studies was initially screened based on title, abstract and the full manuscript. Published studies were eligible for inclusion if they reported the use of ETGBD for the treatment of acute cholecystitis. Studies that evaluated technical and clinical success, along with procedure related adverse events were included. Articles were excluded if they were not available in English, or if they did not have reported outcomes. In studies that compared multiple methods of treatment for acute cholecystitis, data from the cohort of patients who underwent ETGBD were collected and analyzed. Each article title and abstract was reviewed by two investigators (Jandura DM and Puli SR). They obtained full articles that met the inclusion and exclusion criteria, and after an independent review of the full content of each article, they extracted the data. Any differences were resolved by mutual agreement. The agreement between reviewers gave a Cohen’s κ 1.0.

Data extraction and quality assessment

The following data was independently abstracted into a standardized form: Study characteristics (primary author, year of publication), study design, baseline characteristics of study population (number of patients enrolled, patient demographics) and intervention details (procedure indications) and outcomes (technical and clinical success, adverse events). The risk of bias was rated by two authors independently.

Outcome definition

The primary outcome of interest was assessment of ETGBD efficacy in terms of technical and clinical success. Clinical success was calculated based on the cohort of patients that achieved technical success in each study. The secondary outcomes that were assessed were overall and individual procedure related adverse events, and the rates of recurrent cholecystitis following the intervention.

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. First, the individual study proportions was transformed into a quantity using a Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-

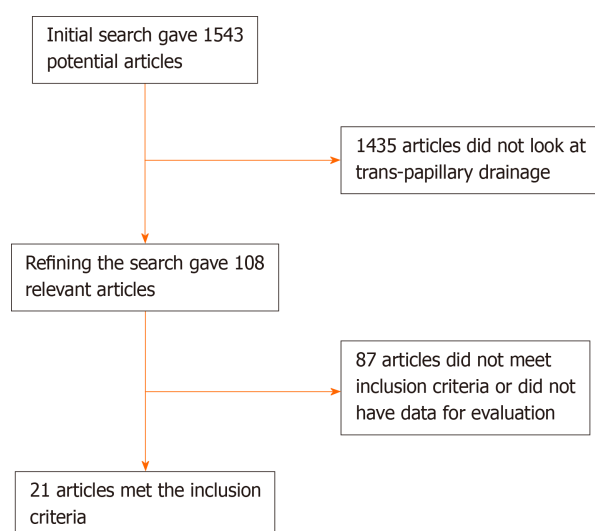


Figure 1 Flowchart of search results.

Laird weights for the random effects model[14,15]. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the forest plots indicates the assigned weight to that study. The effect of publication and selection bias on the summary estimates was tested by the Harboud-Egger indicator[16]. Also, funnel plots were constructed to evaluate potential publication bias[17,18].

RESULTS

Study selection

In summary, 21 studies identified by our search using the literature databases were included for our analysis. A flow diagram of this systematic review is included in Figure 1.

Characteristics of the included studies

In all, 8 studies were performed in Japan, 6 were performed in the United States, and 4 were performed in South Korea. 3 of the remaining studies included in our meta-analysis were originally performed in Germany, Denmark and Italy. Most of the studies were retrospective, however prospective and one random controlled trial was included.

Participants

A total of 1307 patients from 21 studies were included in the meta-analysis. In this meta-analysis, 61.44% of the patients included were males and 38.56% were females. The median age of study subject was 68.41 (range: 48.5-79.7).

Interventions

ETGBD was performed in inoperable patients with acute cholecystitis with placement of a double pigtail stent in 57.1% of studies. Plastic stents were used in 40.0% of studies. Nasobiliary stenting was performed in 45.0% of the studies included in the meta-analysis.

Outcomes

Technical success was reported by all the studies included in the analysis. The prevalence of successfully performed procedures ranged from 70.59%-100%. The pooled rate of technical success of ETGBD was 82.62% [95% confidence interval (CI): 80.63-84.52]. The individual study rates and the pooled proportion of technical success is shown as a forest plot in Figure 2.

Efficacy

Procedure efficacy, as represented by clinical success was described by all the studies

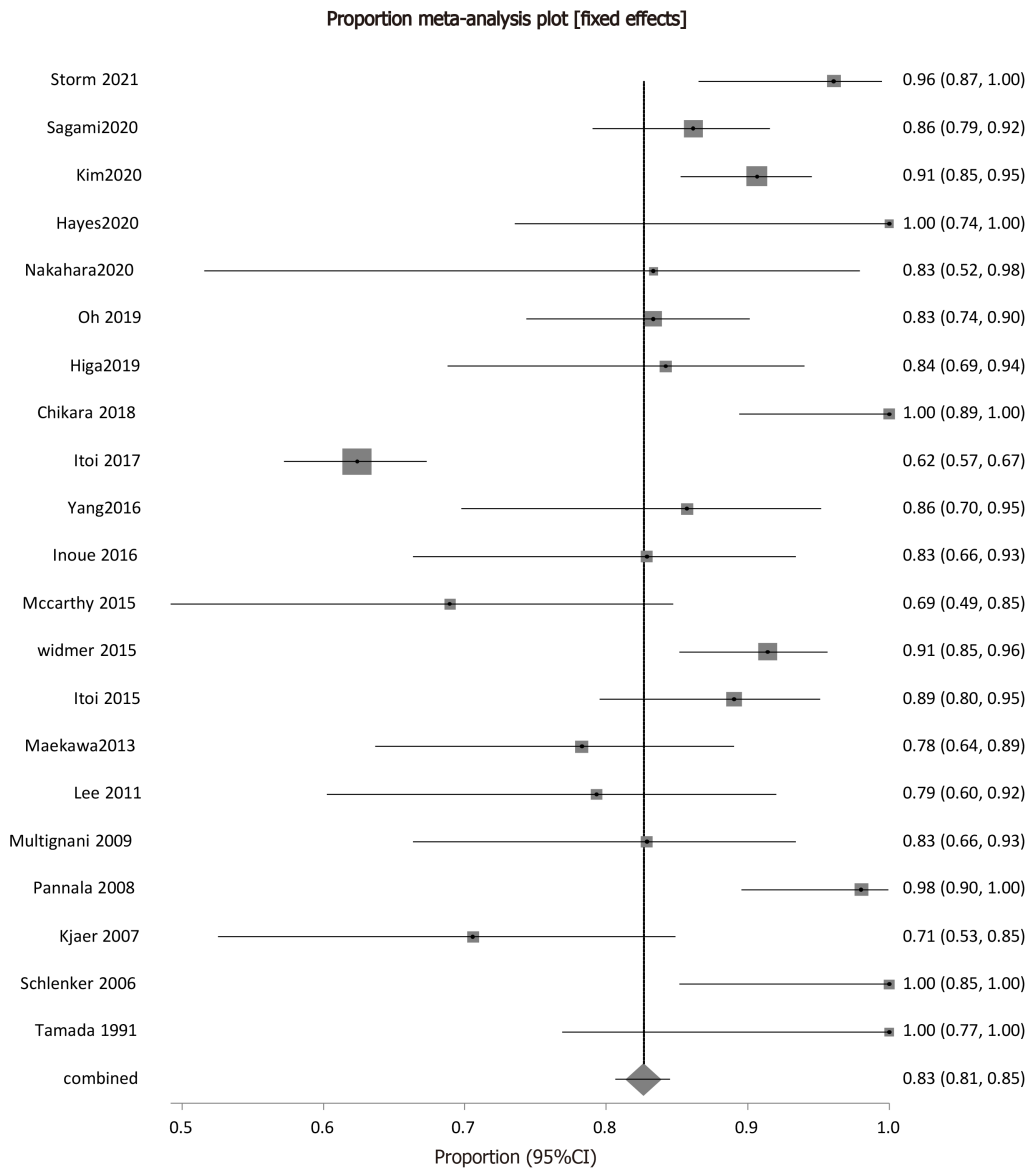


Figure 2 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage technical success in relation to the pooled rate[7,9,22,24-40].

included in the analysis. Prevalence of ETGBD efficacy in successful treatment of cholecystitis ranged from 64.29%-100%. The pooled proportion of clinical success of ETGBD was 94.87% (95%CI: 93.54-96.05). **Figure 3** shows the forest plot of the pooled proportion of clinical success.

Safety

The overall pooled rate of post procedural complications was 8.83% (95%CI: 7.42-10.34). The forest plot depicting the pooled proportion of complications is in **Figure 4**. The pooled proportion of patients with bleeding as an adverse event following ETGBD was 1.03% (95%CI: 0.58-1.62). Pooled proportion of patients with perforation as an adverse event following ETGBD was calculated as a pooled proportion and was 0.45% (95%CI: 0.17-0.87). The pooled proportion of patients with pancreatitis following ETGBD was 1.98% (95%CI: 1.33-2.76).

Stent related procedure complications were also featured in the analysis as adverse events in all the included studies. They included both stent occlusion and stent migration. The pooled proportion of patients with stent occlusion following ETGBD was 0.39% (95%CI: 0.13-0.78). The pooled proportion of patients with stent migration was 1.3% (95%CI: 0.75-1.99).

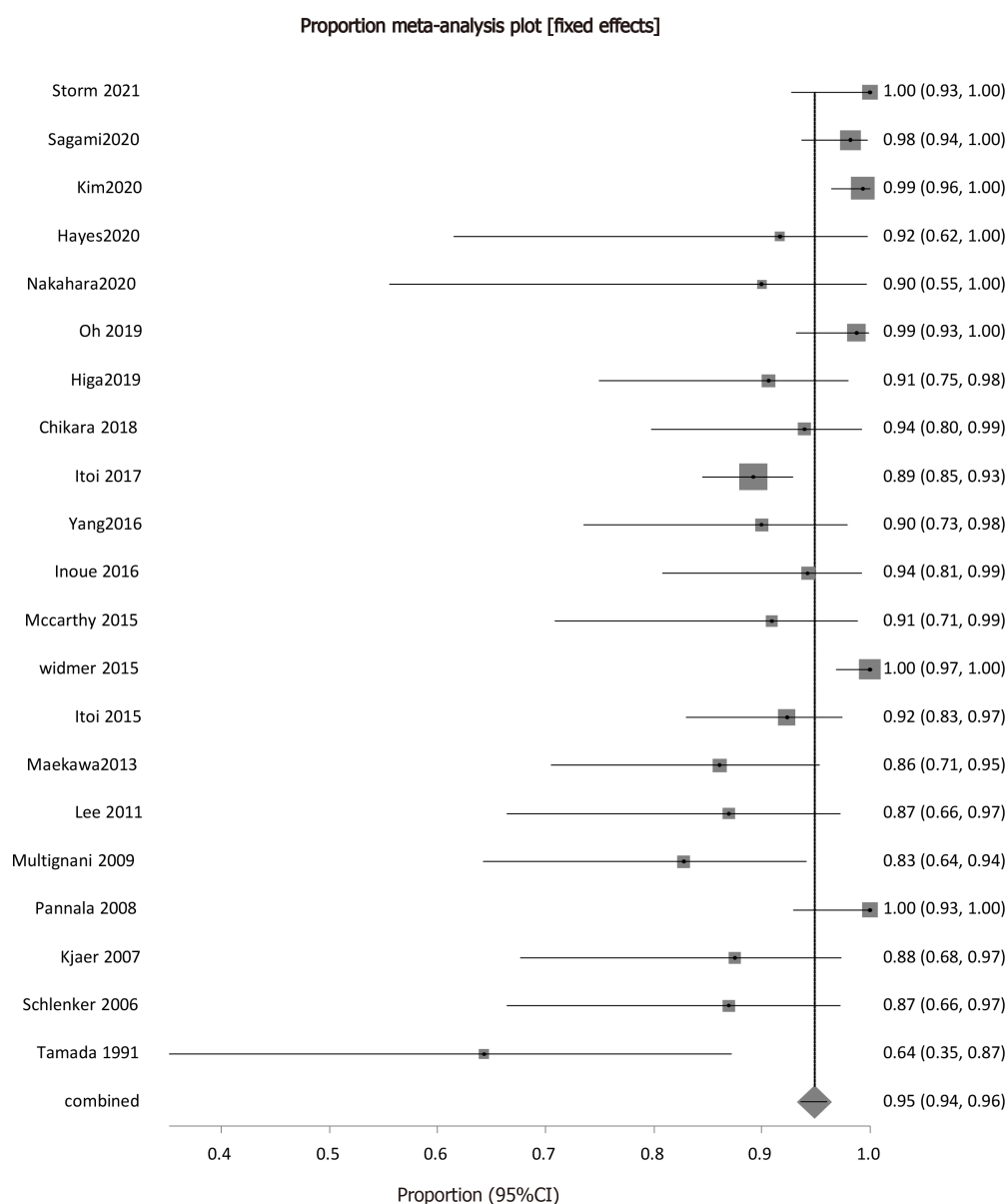


Figure 3 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage clinical success in relation to the pooled rate[7,9,22,24-40].

Recurrent cholecystitis was also included as a secondary outcome measure. There were 6 studies which reported a recurrence of cholecystitis following ETGBD. The pooled proportion of patients with recurrent cholecystitis following ETGBD was 1.48% (95%CI: 0.92-2.16).

Publication bias calculation using the Harbord-Egger bias indicator gave a value of -1.61 (95%CI: -4.70-1.49) ($P = 0.29$), indicating that there was no publication bias. The funnel plot in Figure 5 shows no publication bias for ETGBD clinical success.

DISCUSSION

Cholecystectomy is the standard of care for the treatment of acute cholecystitis, however a subset of patients exists with co-morbidities or poor clinical status that are not candidates for surgery. Based on Tokyo guidelines from 2018, the standard non-surgical approach recommendation for high-risk patients has been percutaneous guided gallbladder drainage[19]. It has remained the most frequently used intervention for inoperable patients due to the vast procedural expertise that exists as well as its significant representation within the literature. The management of cholecystitis has evolved to include endoscopic methods of treatment, and choosing the appropriate intervention requires consideration of multiple factors including

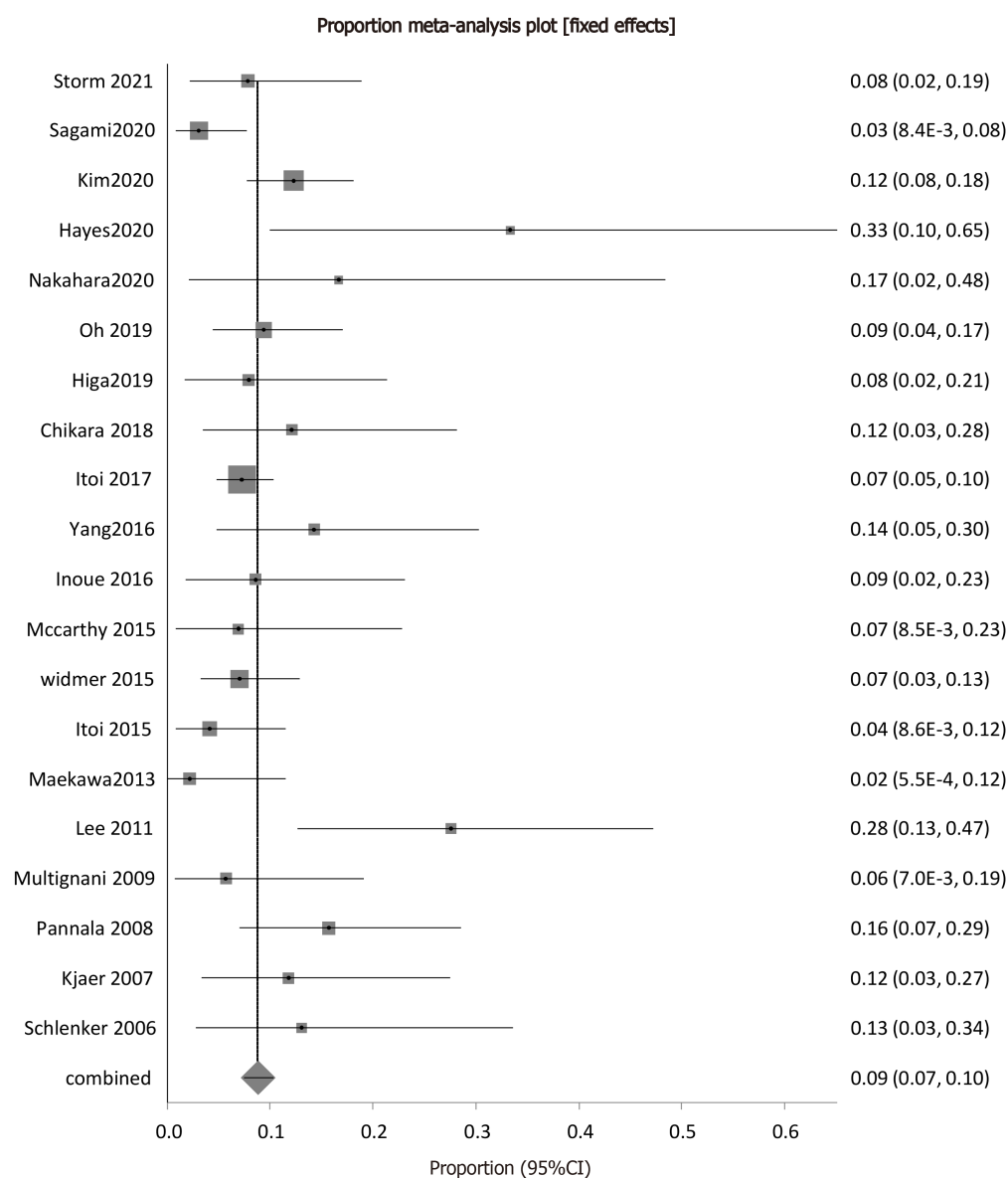


Figure 4 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage related adverse events in relation to the pooled rate[7,9,22,24-39].

patient co-morbidities and preferences, technical factors, and local expertise. Endoscopic therapies have been advantageous over percutaneous drainage when tolerability of externalized drainage is an issue due to patient discomfort and given the potential for these drains to migrate, occlude or become secondarily infected. Other patient factors such as ascites or coagulopathy also need to be considered. Technical factors such as suspected biliary obstruction due to choledocholithiasis and biliary stricture, also support the preferential use of transpapillary gallbladder drainage.

Transpapillary drainage can be technically challenging, specifically due to the difficult nature of cannulation of the bile duct and traversal of the cystic duct. Our pooled rates of technical and clinical success were 83% and 95% respectively. Rates of initial failure are not negligible, however if successfully performed the vast majority of patients found clinical success. Studies have shown that centers with high volume and expertise have benefited from their increased experience, with improved technical success rates. Kjaer *et al*[20] demonstrated an improvement in technical success from 50% in the first 4 years of the study to 89% in the final 5 years of the study, indicating that there is a learning curve that could be overcome with experience. Prior studies have demonstrated similar results when evaluating efficacy of endoscopic drainage in regards to technical and clinical success compared to percutaneous methods[21], though further comparison trials are required.

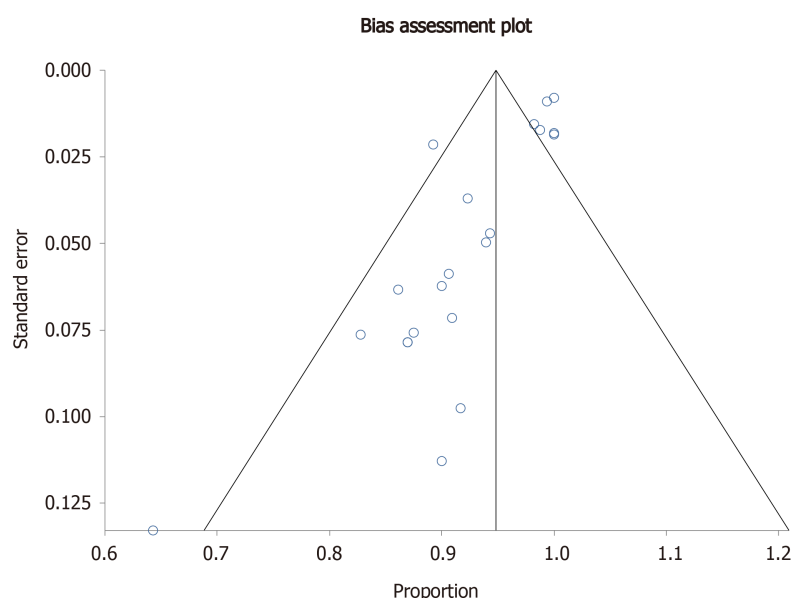


Figure 5 Funnel plot evaluating the effect of publication bias on individual studies rates of endoscopic transpapillary gallbladder drainage success.

Lyu *et al*[23] demonstrated that the adverse event and mortality rates amongst EUS guided gallbladder drainage, transpapillary gallbladder drainage and percutaneous gallbladder drainage were comparable. Nonetheless, post-operative complications related to endoscopic interventions such as EUSGBD and ETGBD tended to have higher risk adverse events that had a higher propensity to lead to death, such as perforation, bleeding, and pancreatitis. Our overall pooled complication rate was about 9%, with the highest being pooled rates of pancreatitis. ERCP related complications have been an increased concern, given the need for cannulation of the bile duct for successful transpapillary gallbladder drainage and stenting to occur. Given the burden of potentially severe adverse events, ETGBD should be reserved for patients who are otherwise not candidates for standard percutaneous drainage. Such therapies should also be performed in centers with high expertise and specifically when other biliary interventions are called for, such as in the case of concomitant choledocholithiasis.

Based on our results, recurrent cholecystitis occurred in about 1% of patients undergoing transpapillary drainage and stenting. These patients with recurrence may require repeat transpapillary drainage, or other methods of gallbladder drainage. A subset of patients can eventually undergo definitive cholecystectomy when clinically stabilized. A particular benefit of ETGBD over other endoscopic interventions such as EUS guided stenting is the avoidance of creating a chole-duodenal or gastric fistula, which can make eventual surgical intervention difficult. Stents placed during ETGBD may be removed just prior to planned cholecystectomy.

Our study had several limitations. Most of the studies included were retrospective analysis, with only one randomized controlled trial. This could have led to selection and time bias. The exclusion of non-English studies could have also led to bias. Inclusion of these studies could have led to more randomized control trials in our analysis. Many of the studies included in the pooled analysis, included the use of nasobiliary drainage. Over the past several years, this method that has been utilized less frequently, in favor of double pigtail stents making the application of our data to everyday practice more difficult. Though based on prior subgroup analysis, double pigtail stenting was compared to nasobiliary drainage with similar rates of technical (85% *vs* 81%), and clinical success (95% *vs* 93%)[21]. Outcome definitions, including technical success and clinical success varied among the included studies. This may have confounded the pooled results, though publication bias was not significant based on indicators that were used.

CONCLUSION

In conclusion, our study supports that ETGBD is a safe and efficacious procedure for

inoperable patients with cholecystitis. Given its relative technical difficulty, which is inherent to ERCP, it should be performed in high volume centers and when patients are unfit for percutaneous drainage. Its clinical success rates were comparable to prior analyses, and rates of adverse events were acceptable. At this time further data and prospective trials would be beneficial in evaluating the long-term outcomes of ETGBD.

ARTICLE HIGHLIGHTS

Research background

Percutaneous gallbladder drainage has been the standard treatment of acute cholecystitis in patients who are not surgical candidates. Our study sought to evaluate the efficacy and safety of transpapillary drainage for acute cholecystitis in this subset of patients.

Research motivation

The key topics of interest include non-surgical, less-invasive techniques to treat acute cholecystitis. The evolution of safe and effective treatments in acute cholecystitis can lead to improved patient outcomes and quality of life following treatment. Future research can also have a positive effect on cost effectiveness and health care utilization.

Research objectives

The main objectives were to evaluate feasibility, efficacy and safety of transpapillary gallbladder drainage in inoperable patients for the treatment of acute cholecystitis. This can positively affect further research and direct comparison trials.

Research methods

A systematic review was performed followed by updated meta-analysis.

Research results

The pooled technical success rate of endoscopic transpapillary gallbladder drainage (ETGBD) was 82.62% [95% confidence interval (CI): 80.63-84.52]. The pooled clinical success rate was found to be 94.87% (95%CI: 93.54-96.05). The pooled overall complication rate was 8.83% (95%CI: 7.42-10.34). Pooled rates of post procedure adverse events were bleeding 1.03% (95%CI: 0.58-1.62), perforation 0.78% (95%CI: 0.39-1.29), peritonitis/bile leak 0.45% (95%CI: 0.17-0.87), and pancreatitis 1.98% (95%CI: 1.33-2.76). The pooled rates of stent occlusion and migration were 0.39% (95%CI: 0.13-0.78) and 1.3% (95%CI: 0.75-1.99) respectively. The pooled rate of cholecystitis recurrence following ETGBD was 1.48% (95%CI: 0.92-2.16).

Research conclusions

Our results demonstrated that transpapillary gallbladder drainage for treatment of acute cholecystitis is both an efficacious and safe procedure in patients that are inoperable. This particular method of gallbladder drainage may offer an alternative to a certain subset of inoperable patients who are otherwise not candidates for percutaneous drainage. Patients who demonstrate signs of concomitant choledocholithiasis or cholangitis also benefit. Comparison between percutaneous drainage, and endoscopic drainage methods with endoscopic ultrasound or a transpapillary approach has been explored however results remain inconclusive.

Research perspectives

Future research should involve randomized controlled trials to compare the different non-surgical techniques used in treatment of acute cholecystitis. In regards to ETGBD, emphasis should be placed on different stenting methods, along with assessment of long term outcomes.

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