ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2018 October 16; 10(10): 225-321

Published by Baishideng Publishing Group Inc

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 10 Number 10 October 16, 2018

WJGE

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Contents

Monthly Volume 10 Number 10 October 16, 2018

SYSTEMATIC REVIEW

ABOUT COVER

AIM AND SCOPE

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WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

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INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy (*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.

EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/1948-5190/editorialboard.htm

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PUBLISHER
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7901 Stoneridge Drive, Suite 501,
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PUBLICATION DATE
October 16, 2018

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 225-238

DOI: 10.4253/wjge.v10.i10.225

ISSN 1948-5190 (online)

REVIEW

Introduction of endoscopic submucosal dissection in the West

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Author contributions: Stavropoulos SN is the source of material for this manuscript; Friedel D formulated it into this manuscript.

Conflict-of-interest statement: Dr. Friedel and Dr. Stavropoulos have nothing to disclose.

Manuscript source: Invited manuscript

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Received: April 27, 2018
Peer-review started: April 27, 2018
First decision: May 16, 2018
Revised: July 21, 2018
Accepted: August 1, 2018
Article in press: August 1, 2018
Published online: October 16, 2018

Abstract

Endoscopic submucosal dissection (ESD) is well established in Asia as a modality for selected advanced lesions of both the upper and lower gastrointestinal tract, but ESD has not attained the same niche in the West due to a variety of reasons. These include competition from traditional surgery, minimally invasive surgery and endoscopic mucosal resection. Other obstacles to ESD introduction in the West include time commitment for learning and doing procedures, a steep learning curve, special equipment, lack of mentors, cost issues, interdisciplinary conflicts, concern regarding complications and lack of support from institutions and interfacing departments. There are intrinsic differences in pathology prevalence (*e.g.*, early gastric cancer) between the two regions that are less conducive for ESD implementation in the West. We will elaborate on these issues and suggest measures as well as a protocol to overcome these obstacles and hopefully allow introduction of ESD as a tenable option for appropriate patients.

Key words: Endoscopic submucosal dissection; Gastric cancer; Barrett's esophagus; Endoscopy training; Colon cancer; Rectal cancer

Core tip: Endoscopic submucosal dissection (ESD) is a well-accepted and widely employed modality in Asia for resection of advanced mucosa-derived lesions of the gastrointestinal tract including early cancer However ESD is not widely utilized in the West for a variety of reasons including lack of mentors, steep learning curve, cost issues and concern for complications. The authors describe these obstacles to the implementation of ESD in the West and measures to overcome them and begin an ESD program. We give a Western perspective on the current status of ESD for lesions of the esophagus, stomach and colorectum.

Friedel D, Stavropoulos SN. Introduction of endoscopic

submucosal dissection in the West. *World J Gastrointest Endosc* 2018; 10(10): 225-238 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/225.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.225

INTRODUCTION

Endoscopic submucosal dissection (ESD) has enabled resection of larger and more histologically advanced epithelial - based lesions including early cancer of the upper and lower gastrointestinal tract as well as a broad array of submucosal lesions, that previously had necessitated surgical removal. ESD allows *en-bloc* resection with precise pathological staging and potential cure. It was invented in Japan where now it is well-established and subsequently permeated into the other East Asian areas[1]. ESD has been slow to be adopted in the West, and its penetration in the United States is especially poor. This disparity regarding ESD availability and implementation respectively in the East and West has had extensive examination with perspective from both areas[2,3]. However, ESD may have finally arrived in the West as it is now critically reviewed in mainstay American gastroenterology journals[4,5].

ESD is a minimally invasive endoscopic/surgical procedure technique for curative resection of advanced lesions including early gastrointestinal (GI) cancer. If curative, it can obviate surgery (laparoscopic or open) that otherwise would be needed for resection. This essence of the value of ESD is less obvious when comparisons are made to endoscopic mucosal resection (EMR) rather than to surgery. The value of ESD is more enhanced when early GI cancer is readily identified at endoscopy. This is arguably done better in the East (especially Japan) where the endoscopist is more apt to spend more time examining the entire gastric mucosal surface, employ magnification, chromoendoscopy and light filtering technique such as NBI and generally better appreciate the appearance of early GI cancer. The accepted classification systems for early GI cancer emanate predominantly from the East. There are mass screening programs for gastric cancer in Japan (not in the West) with both the endoscopist and pathologist vigilant for early gastric cancer (EGC).

The European Society of Gastrointestinal Endoscopy (ESGE) consensus guidelines on the role of ESD in the resection of more common mucosal - derived lesions of the GI tract reflect a relatively limited niche[6]. This panel concluded that most rectal and colonic superficial lesions can be effectively removed with traditional snare polypectomy and/or EMR. ESD is considered for colorectal lesions with a significant suspicion of limited submucosal invasion based on an irregular (non-granular) surface or depressed morphology that are not amenable to snare removal. EMR is the preferred approach for removal for Barrett's lesions with curative intent in that ESD has not been demonstrated to be superior. ESD, however, may be considered for Barrett's lesions larger than 15 mm, poorly lifting lesions and lesions with a concern for submucosal invasion. The panel did recommend ESD to achieve endoscopic *en-bloc* resection of superficial esophageal squamous cell cancers with the exclusion of those with obvious submucosal invasion. EMR may be considered for SCC's < 10 mm. ESD, though, was acknowledged as the first option to provide complete resection and accurate pathological staging. Also, ESD was recommended as the treatment of choice for most gastric superficial lesions. EMR may be an acceptable option for lesions < 10-15 mm and low probability of advanced pathology (Paris 0-ⅡA)[6]. Thus ESD is the accepted standard for EGC if tumor size < 2 cm, intramucosal, intestinal gastric cancer histology and no ulceration.

BARRETT'S ESOPHAGUS AND CANCER

The 2015 ESGE guidelines favor EMR over ESD for Barrett's esophagus and early cancer except for larger and more advanced lesions[6]. The two modalities were comparable in terms of recurrence and complication rate with ESD more time consuming[7] (Table 1). In a small randomized controlled trial (20 subjects each group) comparing ESD to EMR for Barrett's high-grade dysplasia or early cancer (< 3 cm), the two groups were comparable again in terms of remission, occurrence and need for surgery[8]. Complete resection was five times more likely in the ESD group, though the two severe adverse events was seen in the ESD group as well. Their compilation of ESD data reflects success with *en-bloc* resection though some series had significant complication rates (Table 2). Some ESD groups had no strictures but others had a stricture rate up to 50%[9-11]! More recent comparative studies and commentary reinforced the feasibility and safety of ESD in the West for BE and EAC with better R0 resection rates than EMR and the de facto choice for larger (> 3 cm), nodular, scarred and ulcerated lesions[12-14].

The Western centers foray into ESD for early esophageal cancer reflects mixed results and a fairly steep learning curve. A multicenter ESD study with resection of HGD or EAC had a R0 resection, curative and stricture rate of 76%, 70% and 15%[12]. Our center's resection experience with resection of cancer (EAC and SCC) and HGD yielded an *en-bloc*, R0, curative and stricture rate of 98%, 83%, 74% and 10% respectively (Figure 1). There was a significant decrease in procedure time with experience[15].

ESD in the esophagogastric junction is technically difficult and should be restricted only to higher volume specialized centers. Barrett's is less frequent in Japan where is more overall ESD expertise and this may hinder ESD in its comparison with EMR for BE resection results.

ESD

Early gastric cancer

Five pioneering Western ESD centers detailed their results for resection of gastric cancer[16-20] (Table 3). *En-*

Table 1 Endoscopic mucosal resection *vs* endoscopic submucosal dissection for early Barrett's and esophagogastric junction neoplasia

Outcome	ESD-6 Asian studies No. of studies	*n* (%)	EMR-10 Western studies No. of studies	*n* (%)	Odds ratio (95%CI)	*P*-value
Recurrence rate	6	1/333 (0.3)	5	10/380 (2.6)	8.55 (0.91, 80.0)	0.06
Perforation	6	5/335 (1.5)	9	8/686 (1.2)	1.07 (0.20, 5.62)	0.94
Delayed bleeding	6	7/335 (2.1)	9	8/686 (1.2)	0.46 (0.12, 1.75)	0.26
Stricture	5	7/207 (3.4)	7	3/456 (0.7)	0.21 (0.03, 1.41)	0.11
Method	No. of studies		Pooled procedure time (95%CI)			
EMR	2		36.7 (34.5, 38.9)			
ESD	5		83.3 (57.4, 109.2)			

Modified from Komeda *et al*[7]. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 2 Endoscopic submucosal dissection for Barrett's high-grade intraepithelial neoplasia and early adenocarcinoma

Reference	Chevaux *et al*[9]	Kagemento *et al*[10]	Höbel *et al*[11]	Tergheggen *et al*[8]
Subjects	75	19	22	17
Study design	Retrospective	Retrospective	Retrospective	Prospective
Rates of resection				
En-bloc	90%	100%	96%	100%
R0 resection rate	64%	85%	82%	59%
Curative rate	64%	65%	77%	93%
Adverse events				
Bleeding	3%	4%	9%	0%
Perforation	4%	0%	5%	12%
Stricture	60%	15%	14%	0%

Modified from Terheggen *et al*[7].

Table 3 Endoscopic submucosal dissection for early gastric cancer in the West

Reference	*N*	Follow-up (yr)	Mortality (%)	*En-bloc* resection (%)	Curative resection (%)	Surgery (%)	Recurrence (%)
Cardoso *et al*[16]	15	1	0	80	74	8	8
Catalano *et al*[17]	12	2.5	0	92	92	8	8
Probst *et al*[18]	91	2.3	0	87	72	12	5.6
Schumacher *et al*[19]	28	2	3.4	90	64	7	11
Pimental-Nunes *et al*[20]	136	2.2	0	94	82	7	7

Modified from Oyama *et al*[2].

bloc resection was obtained in over 80% of subjects with 64%-92% achieving cure. However, there was a 10%-20% complication rate with no mortality in 4/5 series and 3% mortality in one series.

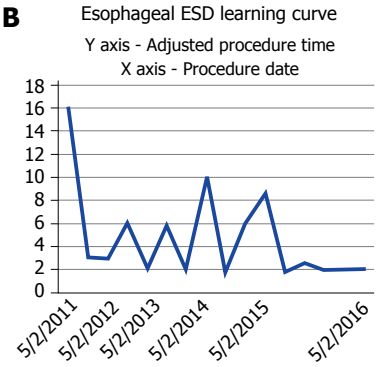
The Japanese suggested expanded criteria for ESD in EGC to include larger lesions (> 3 cm), ulcerated lesions of smaller size (< 3 cm), superficial submucosal lesions < 500 micrometers and possibly diffuse histology EGC if < 20 mm and consistent with absolute criteria above[21] (Table 4). Long-term outcomes of patients with expanded criteria including larger lesions (> 3 cm), ulcerated lesions of smaller size (< 3 cm) have excellent reported results in a Japanese multi-center prospective study[22]. However, enthusiasm in the West for ESD in EGC was tempered by a study demonstrating increased tendency for lymph node metastases in EGC for non-Asian subjects matched to Asian subjects with similar histopathological findings[23]. A German study of EGC subjects having surgery demonstrated a lymph node metastases rate of 21%/16%/40% respectively, for $sm_1/sm_2/sm_3$ tumor extension[24]. Thus, there is debate among European medical societies about extrapolation of the Japanese expanded criteria to European subjects.

A more recent European study validated the success of ESD in EGC even with expanded criteria subjects as well showing improved technical performance with greater speed and better clinical results[25] (Table 5). However, the racial/regional differences issue in EGC still somewhat lingers in that complete resection rates were less than most Asian studies and there was a 1% mortality compared to a negligible rate in Asia. There was a non-statistical superiority of survival of subjects with guideline entry criteria compared to those with expanded criteria but this appeared at 7 years with a 13.2% mortality with guideline criteria and 18.4% with expanded criteria (Figure 2).

A

ESD characteristics *n* = 41	
En-bloc resection, *n* (%)	40 (97.5)
Procedure time (min), median (range)	92 (10-291)
Lesion size (cm), mean diameter (range)	1.9 (0.5-3.9)
Total AEs *n* (%)	8 (20%)
Early AEs (within 24 h)	
Self-limited bleeding (no endoscopy)	1 patient
Prophylactic stent at time of ESD	1 patient
Transient self-limited pain and fever	1 patient
Glue to cover deep mp defect	1 patient
Late AEs (beyond the first 24 h)	
Strictures [all successfully dilated over a median of 3 sessions (1-4)]	4 patients
Histopathology *n* = 41	
RO resection, *n* (%)	7 (17)
at lateral margin	4 (57.1)
at deep margin	1 (14.2)
at both margins	2 (28.5)
Depth of invasion of carcinomas	34 cancers
Adenocarcinoma	
Pt1a	17 (63%)
Pt1b	9 (33%)
pT2 (R0 including superficial muscularis)	1 (4%)
Squamous cell carcinoma	
Pt1a	5 (71%)
Pt1b	2 (29%)

B



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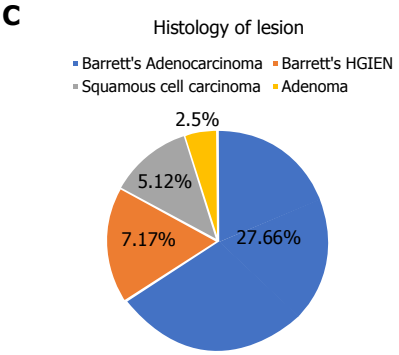

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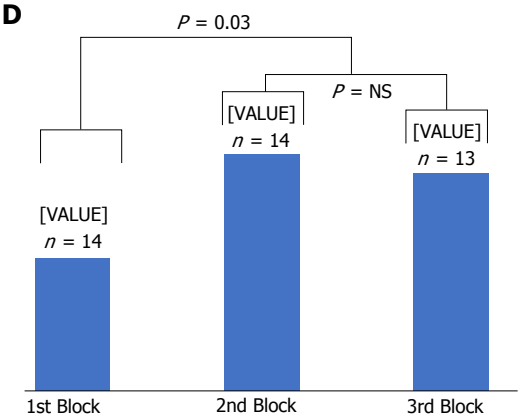

Figure 1 NYU Winthrop esophageal endoscopic submucosal dissection experience. A: ESD characteristics and histopathology; B: Histology of lesions; C: Learning effect on procedure time; D: Learning effect on R0 resection rate. AEs: Adverse events; ESD: Endoscopic submucosal dissection.

Colorectal ESD

The predominance of colon polyps and cancer relative to early gastric cancer in the West would theoretically allow Western physicians to garner needed ESD experience, but unfortunately, Western societal guidelines and thought leaders are not encouraging in this regard. As mentioned, the 2015 ESGE guidelines relegates ESD for colorectal lesions that are larger, likely more invasive or clearly not amenable to EMR[6]. In the United States, Dr. Ginsburg stated: "ESD over EMR for the vast majority of colorectal neoplasms (*i.e.*, adenomas) cannot be reconciled with the increased risk and procedure duration"[26]. Dr Rex stated: "Colorectal ESD, and *en-bloc* resection in general, are powerful concepts that currently come with a high price tag for most American colonoscopists. However, we acknowledge that as with many evolving technologies, deciding whether to learn colorectal ESD is "gray" not "black and white"[27]. Rex's group calculated the NNT for ESD to obviate surgery is 7 which was characterized as "a lot of work" but arguably individual patients may disagree! Moreover, this calculation may be flawed in that they only consider lesions with superficial SM invasion. However, there are two other scenarios where ESD can spare patients from colectomy: Aborted EMR due to fibrosis/non-lifting/difficulty in snare positioning-approximately 5% in Moss[28]) and intractable recurrences after EMR (approximately 2%) Including these scenarios, the NNT may be as low as approximately 5! A cogent argument favoring ESD over EMR is the high relative *en-bloc* resection and potential curative rates. A recent meta-analysis comparing the two modalities favored ESD with pooled odds ratio (OR) for *en-bloc* resection, cure and recurrence respectively of 6.8, 4.3 and 0.08

Table 4 Endoscopic submucosal dissection for early gastric cancer

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	No ulceration		Ulcerated		SM1	SM2
	⩽ 20	> 20	⩽ 30	> 30	⩽ 30	Any size
Intestinal	1	3	3	4	3	4
Diffuse	2	4	4	4	4	4

[1]Guideline criteria for ESD; [2]Consider surgery; [3]Expanded criteria for ESD; [4]Surgery (gastrectomy + lymph node dissection). ESD: Endoscopic submucosal dissection.

Table 5 Major Western endoscopic submucosal dissection series for early gastric cancer *n* (%)

	Guideline criteria	Expanded criteria	Out of indication	*P*-value
179 subjects	53 subjects	87 subjects	30 subjects	
Post ESD endoscopic follow-up	53/53 (100)	84/87 (97)	27/39 (69)	< 0.001
Follow-up median (mo)	51	56	36	NS
Curative resection	47/53 (89)	65/87 (75)	0	0.07
Local recurrence	0	4/84 (5)	3/27 (11)	0.06
Post ESD surgery	0	3/87 (3)	12/39 (31)	< 0.001
Metastases	0	1/84 (1)	3/27 (11)	0.005
Gastric cancer mortality	0	0	3 (8)	0.004
All-cause mortality	7 (13)	16 (18)	11 (28)	0.19

One hundred and seventy-nine ESD procedures for EGC over 12 years-about 15/year (modest compared to Asian centers). This Western center's learning curve: 1st block of ESD's (1-96) compared to 2nd block (97-191). R0 resection increased from 60% (57/96) to 93% (88/95) ($P < 0.001$). Median procedure time decreased from 148 to 110 min ($P < 0.001$). Modified from Probst *et al*[25]. ESD: Endoscopic submucosal dissection; NS: Not significant; EGC: Early gastric cancer.

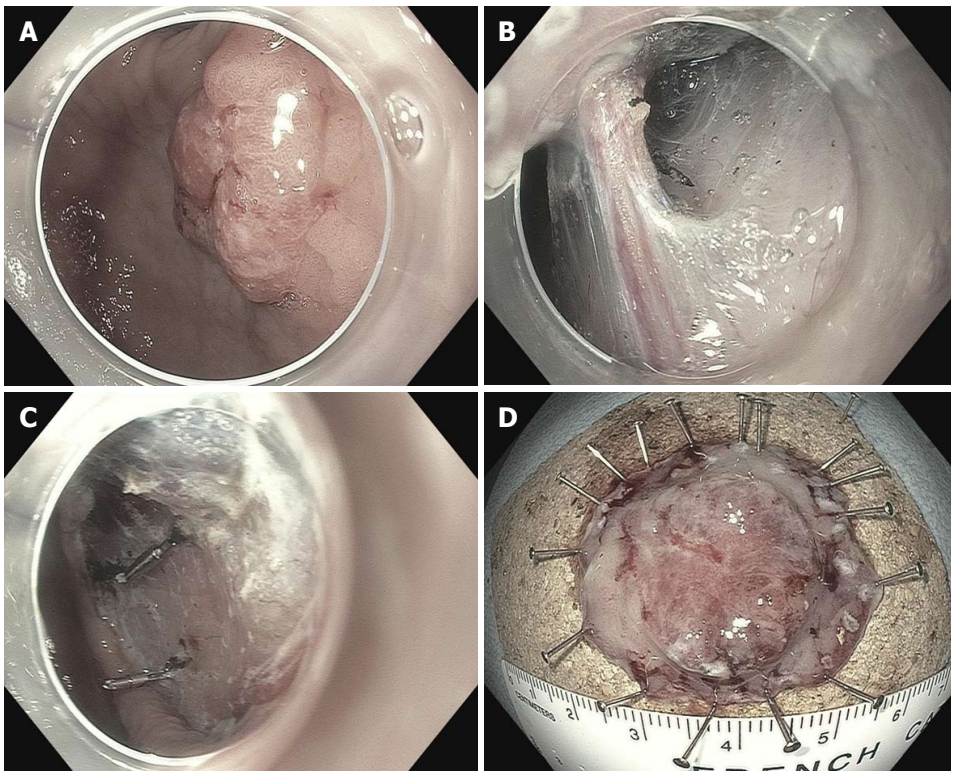

Figure 2 Endoscopic submucosal dissection of early gastric cancer (NYU-Winthrop).

respectively[29]. "Enhanced" EMR with cold snare and water immersion minimally lessened this relative disparity with the cold snare group showing 18% recurrence at 5 mo for lesion > 2 cm[30] and the water immersion group had a 10% recurrence rate for these lesions at 6 mo[31].

Cost analysis comparisons of colon EMR *vs* ESD would favor the former in the short run because of

Table 6 Cost analysis-endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions

ESD *vs* Wide-field EMR for large sessile and lateral spreading lesions > 2 cm: Cost analysis
Selective ESD prevented 19 additional surgeries per 1000 cases at slightly lower cost compared with WF-EMR
U-ESD could prevent an additional 13 surgeries per 1000 cases compared with S-ESD but at substantially increased cost of > 21000 dollars (Australian) per surgery avoided
Expanded ESD criteria (Japanese Gastrointestinal Endoscopy Society) adding mainly granular lesions > 4 cm added little additional benefit
Authors stated U-ESD is "unjustified" given WF-EMR effectiveness for benign lesions of LR-SMIC
Subgroup analysis of only rectal lesions concluded WF-EMR including trans-anal resection was as effective as S-ESD and still less costly
Because of the higher prevalence of SMIC in the rectum, the incremental cost per surgery avoided by U-ESD decreased to $87066 and dropped to $32132 among non-granular rectal lesions. U-ESD became the least costly and most effective strategy among higher risk non-granular Paris 0-is rectal lateral spreading lesions
Study design: Selective ESD strategy was employed for lesions suspicious for SMIC-all others had WF-EMR. Pathology after ESD revealing high - risk SMIC necessitated surgery. LR-SMIC on pathology at the ESD were considered cured

After Behin. *Gut* 2017. U-ESD: Universal ESD; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; LR-SMIC: Low prevalence of low risk submucosal invasive cancer; WF-EMR: Wide field endoscopic mucosal resection; S-ESD: Selective endoscopic submucosal dissection; SMIC: submucosal invasive cancer.

longer procedure time and associated anesthesia as well as need for more expensive equipment with ESD, but ESD is more cost-effective in the long term because of its significantly better curative resection rate with less incumbent need for subsequent surveillance colonoscopy[32]. Another group compared various strategies for sessile lesions and lateral spreading colorectal lesions > 2 cm including wide field EMR (WF-EMR), selective ESD (S-ESD) and universal ESD[33] (Table 6). Selective ESD was performed when there was concern for submucosal invasion including lesions that were non-lifting, Paris 2C in appearance or with Kudo V pit pattern. S-ESD was preferred for all but rectal lesions. However, the study design favored EMR by including 18% rectal lesions, and in earlier work by the same group, there was 16% recurrence after EMR at 4 mo with an additional 4% new recurrences in those patients at 16 mo for a total of 20% cumulative recurrence by 16 mo[28]. For ESD, recurrence rate in a meta-analysis of 104 colorectal ESD studies[34]: 1% at 19 mo and 0.04% if R0 resection! In another meta-analysis[35] comparing colon EMR *vs* ESD, recurrence was 0.9% for ESD.

Starting an ESD program

The Western ESD pioneers will likely have their R_0 resection rates and significant complications closely scrutinized by their gastroenterology colleagues, surgeons, tumor boards and administration (Table 7). Cost-effectiveness will be an ongoing debate at most institutions but, if curative resection and significant AE rate are satisfactory, one can effectively advocate for ESD by emphasizing the benefits of having an ESD program (Table 8). Enhanced EMR methods such as circumferential mucosal incision (CMI) or circumferential submucosal incision (CSI) followed by snare removal have not shown R_0 or curative resection rates comparable to traditional ESD but can help build ESD skills[36,37]. The performance of ESD is often a multi-hour endeavor and anesthesia, nursing and ancillary personnel should be aware of their roles. Ergonomic consideration should be given to both the operator and the patient-two deaths in a European study may have related to thrombosis[6,38,39]. In addition, both the patient and pathology should be appropriately triaged (Table 7). Appropriate medical or other discipline clearance should be obtained beforehand. Endoscopic and pathologic data should be evaluated with caution. Concordance of biopsy and resected specimen pathologic diagnosis of gastric polyps > 5 mm is only 55%-77%[40,41]. Concordance of biopsy and resected specimen pathologic diagnosis of colon polyps in one study was only 60%[42].

There are progressive phases or stages typically necessary for development of ESD skills. Initially, one acquires basic knowledge *via* texts, reviews and courses. Lesions should be properly assessed including use of enhanced imaging. Knowledge of electrosurgical generators and their appropriate settings for the various ESD stages as well as familiarity with the common electrosurgical knives. Overall, one should develop an understanding of ESD techniques, indications, limitations, risks and expected outcomes. Subsequently, training can be obtained in *ex vivo* animal models including pig esophagus/stomach and bovine rectum. Expenses may be possibly defrayed by industry support in anticipation of equipment necessary for an ESD program. Before embarking on ESD cases in humans, one should observe live ESD cases by experts; probably a minimum of 20 cases. Trainees can likely assist in ESD cases by their mentor experts. A trip to Japan with concentrated exposure and ideally hands-on experience can also be useful[43]. These experts may also travel to regional meetings. Experts may also view a video of your technique with suggestions[44]. The 2010 ESGE White Paper suggested performance of 30 ESDs reaching speed of 30 min/5 cm lesion in live animals as well as management of simulated complications such as bleeding and perforation prior to clinical ESD[45,46].

Once the operator begins to perform clinical ESD, there must be a sufficient volume of cases to maintain and improve techniques. This would be a minimum of two cases per month but preferably at least a case weekly[2,47]. In the "step-up" approach of transitioning from clinical training to competence, one would do

Table 7 Caveats for the endoscopic submucosal dissection pioneer

Start clinical ESD only after extensive pre-clinical training
Start with easier lesions
Avoid "unprincipled ESD"
Record and monitor closely outcomes and complications- consider registry and videos
Be familiar with techniques for endoscopic management of complications
The main complications (perforation and bleeding) can almost always be managed (or even prevented in the case of bleeding) by skillful application of clips and coagulation
Experience with endoscopic clip placement and coagulation grasper application is essential (experience with endoscopic suturing is highly desirable)
Avoid mistakes in selecting and scheduling cases-many referral reports lack detailed information on morphology, size, location, prior manipulation
Morphology (*e.g.*, Paris classification) may suggest a more advanced lesions that was appreciated on the index endoscopy and biopsy that may require expedited scheduling
Index biopsies may be misleading (obtained from the periphery rather than depressed areas of 2c or 1s lesions missing a carcinoma)
Biopsies yielding only dysplasia may result in a publicly delayed resection of cancer
Concordance of biopsy results and ultimate post-resection pathology is fair at best
EDUCATE your referring physicians-AVOID inappropriate India ink tattooing and "partial snare resections"/hot forceps/jumbo forceps for "diagnosis or "attempted" hasty resections (tackling lesions where probability of complete EMR is low)
Lack of experience in delineating early GI cancer main lead to excessive sampling biopsies
DISCOURAGE APC to" vaporize "grossly" evident residual tumor or aggressive/many biopsies of delicate flat lesions (SSA's)
ENCOURAGE: (1) detailed descriptions: size, morphology; (2) lots of pictures; (3) giving print out with color pictures to the patient and d) having referring physicians transit "money" shots of lesion to you
Put post - resection specimens on corkboard and educate pathologist about specifics of resection
Pathologists should properly orient specimens with ⩽ 2 mm slices
Pathology report should comment on adequacy of resection including deep and lateral margins with measurement of submucosal invasion with micrometer measurements as well as the differentiation (G1-G3)
Optimally there should be desmin staining of the muscularis mucosa noting the pattern of SM invasion, *e.g.*, budding
Comment should be made regarding lymphovascular invasion with elastin Van Gieson stain to delineate venules and the D2 – 40 immunostain for lymphatics (important)
Multidisciplinary input and communication including nursing, technicians, anesthesiologists, surgeons and oncologists
The patient should be evaluated as dictated by medical history by internists, cardiology and pulmonary medicine with particular attention to anticoagulants and antiplatelet drugs
Ergonomic considerations are given to both ESD operator and patient

ESD: Endoscopic submucosal dissection; GI: Gastrointestinal.

Table 8 Benefits of institution endoscopic submucosal dissection program

Potential benefit in avoiding surgery/organ resection
"Downstream revenue "from increased services and subsequent referral to surgery/oncology of patients (possibly up to 20% of ESD's performed)
Enhancement of overall institutional prestige
ESD is a necessity for any institution purporting to be a tertiary referral center for luminal GI tract
Enhanced recruitment of trainees and faculty after establishment of ESD program

ESD: Endoscopic submucosal dissection; GI: Gastrointestinal.

20-30 supervised cases-optimally in the antrum or rectum where management of complications is easiest with a subsequent 20-30 cases in more challenging areas with the goal of achieving > 80% *en-bloc* resection and < 10% complications in 20 consecutive cases[45]. The next phase is the transition from competence to proficiency-usually > 80 cases. This is mostly a result of self- training to attain proficiency with an *en-bloc* resection rate ⩾ 90% and dissection speed ⩾ 9 cm^2/h. "Master classes" and/or additional observation of live cases by experts may help at this stage (refine skills and acquire more advanced tips and tricks). The next and last phase is mastery after hundreds of cases with a curative rate > 80% and teaching of other physicians. The difficulty of ESD varies by location with the proximal stomach, colon flexures and ileocecal valve/appendiceal areas and ESD in the small intestine including the duodenum reserved for true experts (Figures 3 and 4).

CHALLENEGES FOR WESTERN ESD OPERATOR

The Western ESD operator is at a distinct disadvantage compared to his Asian counterpart with the latter having widespread acceptance, existent infrastructure, choices of mentors and ample pathology. In the West, the relative paucity of early gastric cancer cases relative to colon and esophageal pathology is a particular challenge. As mentioned, the Western endoscopist may be less attuned to the appearance of EGC. There are about eight times more cases of gastric cancer in Japan than in the United States[48]. SEER database analysis over a recent decade in the United States noted 43769 cases of gastric adenocarcinoma of which

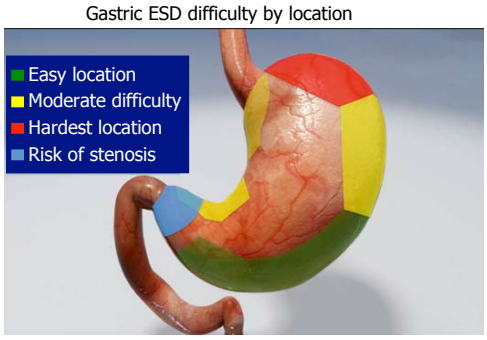

Figure 3 Gastric endoscopic submucosal dissection difficulty by location. ESD: Endoscopic submucosal dissection.

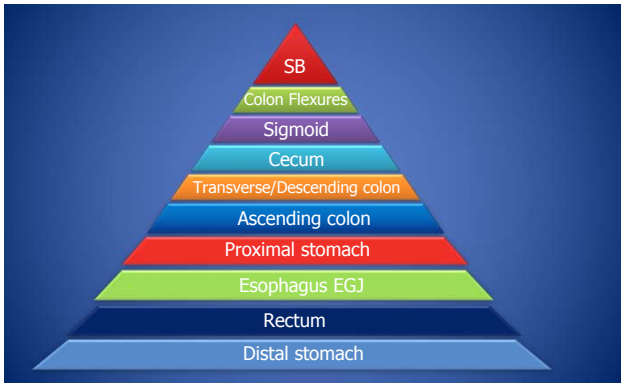

Figure 4 Relative endoscopic submucosal dissection difficulty by location. ESD: Endoscopic submucosal dissection; EGJ: Esophagogastric junction.

1826 were EGC-only 203 cases yearly[49]! Absence of suitable lesions was the main perceived obstacle to ESD implementation in the West as per a survey of 40 ESD trainees at a conference[50]. There are different approaches in the West to this obstacle of too few EGC cases. The "step-up" approach for "untutored learning" in the West recommends starting with UGI lesions where ESD is easier and most beneficial (resecting early cancers). But this approach is problematic for several reasons. UGI lesions are rare (unlike colon lesions) and would make it difficult to achieve the 2 lesions/mo requirement. An R1/Rx resection (a common error during ESD learning) is much more detrimental in the UGI tract than in the colon; especially if high risk colon lesions are avoided during learning. For UGI lesions (often carcinomas) patient would be subjected to highly morbid surgery (esophagectomy/gastrectomy) whereas for colon adenomas/HGIEN careful follow-up/ further endoscopic treatment is sufficient for most R1 resections[51].

Another approach to the relative paucity of early gastric cancer in the West for the ESD operator is to have a prevalence based or ad hoc strategy[51]. Berr described this relatively untutored ad hoc strategy where 80% of his first 50 cases were in the colorectum, and he clearly documented improved rates of *en-blo* and R_0 resection as well as a lower perforation rate and increased speed of dissection with increasing experience[51]. A South Korean study of colorectal ESD without prior gastric ESD experience noted the same positive trends as the Berr group with more cases and the performance > 100 ESDs, rectal ESD and lack of submucosal fibrosis were independent predictors of success[52]. Competence was defined as 80% *en-bloc* resection rate and statistically significant decrease in operative time[53]. An Italian endoscopist with prior EMR experience did not transition to colon ESD until ESD competence was demonstrated in the rectum[54]. All lesions were > 2 cm, and again increased *en-bloc* resection rates were noted with increased experience as well as decreased operative time, but defined competence was noted after only five cases in the rectum but required 20 cases in the colon[54].

NYU Winthrop ESD experience

The NYU Winthrop ESD experience was also untutored with gradual progression of skills (Figure 5). There was progression from ESD to natural orifice translumi-nal endoscopic surgery (NOTES) including POEM, submucosal tunnel endoscopic resection (STER) and endoscopic full-thickness resection (EFTR)[55]. The initial four year experience reflected the learning curve with 53% and 75% *en-bloc* resection rates respectively for early mucosal neoplasms and submucosal tumors[56] (Table 9). We studied the relative utility of various electrosurgical devices during this period[57]. We have performed over 500 ESD's with progressively faster dissection rate and presently an *en-bloc* resection > 90% (Figure 6). We have resected early mucosal neoplasms and submucosal lesions from the esophagus, stomach, duodenum and colorectum as well as ileocecal valve polyps that extended into the ileum[55,56].

ESD complications

The significant adverse events of hemorrhage and perforation are more common in ESD then with EMR, and a major concern for the fledgling ESD operator, though, as mentioned, the complication rate diminishes usually with experience and likely is better managed by the more seasoned operator[46,50]. The ESD resection bed should be copiously irrigated to assess for vessels that may cause subsequent post - resection bleeding. The main complications (perforation and bleeding) can almost always be managed (or even prevented in the case of bleeding) by skillful application of clips and coagulation Experience with endoscopic clip placement and coagulation grasper application is essential (experience with endoscopic suturing is highly desirable) (Table 7). There is controversy as to the necessity of closing the ESD post-resection defect. Proponents of closure cite less delayed bleeding and perforation as well as earlier discharge with associated decreased cost, but the data is limited to date[58]. Opponents argue that closure may complicate subsequent surveillance or further resection at the ESD site by creating artificial

Table 9 Western Center initial endoscopic submucosal dissection series *n* (%)

EMNS		SETs	
Total Lesions	38 (43)	Total lesions	51 (57)
Size, mean millimeters (range)	26 (5-90)	Size, mean millimeters (range)	18 (8-55)
Complete *en-bloc* resection (R0 deep + lateral margins)	20 (53)	Complete *en-bloc* resection (completeness assessed endoscopically)	38 (75)
		Complete 2-piece resection	5 (10)
		incomplete resection	8 (15)
Histologic diagnosis		Histologic diagnosis	
T1 carcinomas/adenomas with HGD	16 (42)	GIST	12 (23)
Adenomas w/o HGD	10 (26)	Pancreatic rests	11 (21)
No residual adenoma granulation tissue	11 (29)	Lipomas	8 (16)
Unclassified	1 (3)	Carcinoids	6 (12)
		Granular cell tumors	3 (6)
		Leiomyomas	8 (16)
		Other	3 (6)

SETs: Subepithelial tumors; EMNS: Early mucosal neoplasm; GIST: Gastrointestinal stromal tumors; HGD: High grade dysplasia.

Figure 5 Chronology of endoscopic submucosal dissection development in a Western Center. ESD: Endoscopic submucosal dissection; STER: submucosal tunnel endoscopic resection; EFTR: endoscopic full-thickness resection.

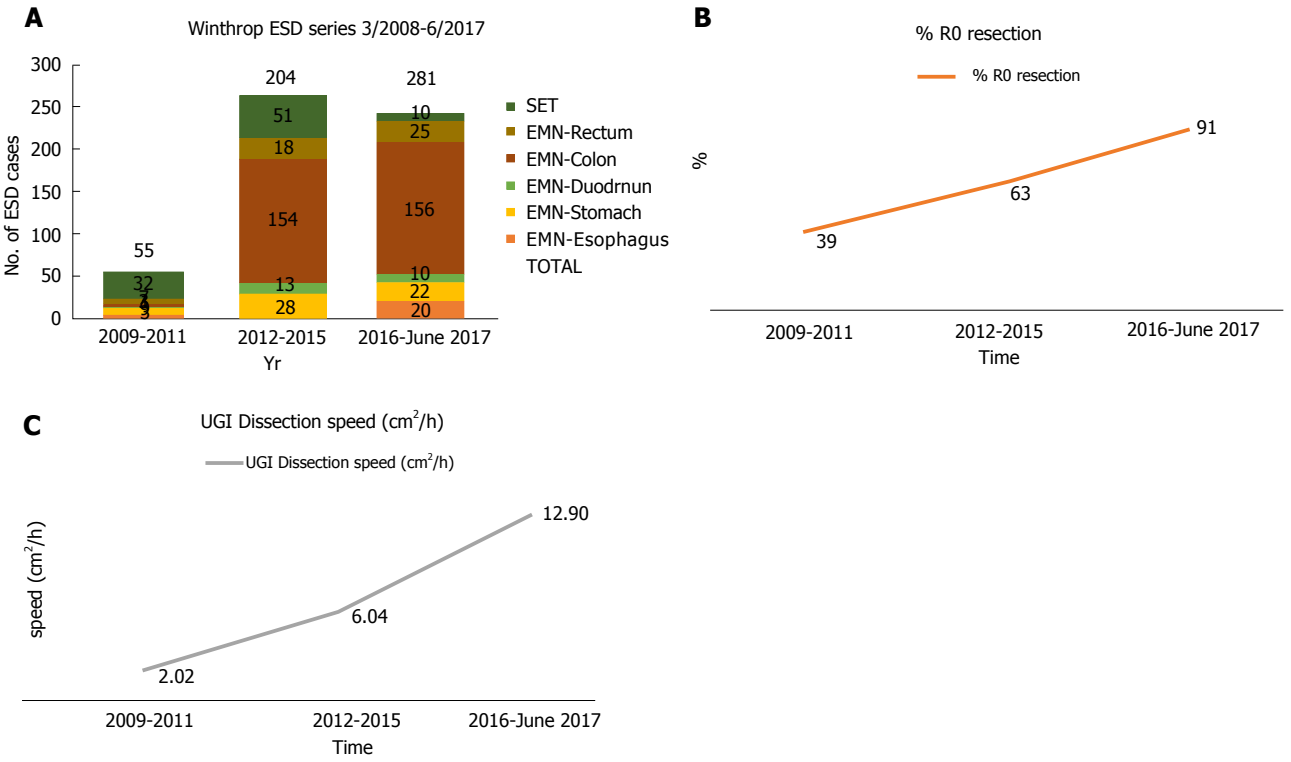

Figure 6 NYU-Winthrop endoscopic submucosal dissection experiences. A: ESD pathology; B: ESD R0 rates; C: UGI ESD dissection speed. ESD: Endoscopic submucosal dissection.

nodules or other "lesions" and/or burying residual neoplastic tissue and questionable cost-effectiveness[59]. Use of an omental patch may help in perforation closure either with clips or endoscopic sutures. Berr noted the relatively low rate of colonic ESD complications in early operators reported in the Japanese literature (< 12.5%) may not extrapolate to the Western experience[51]. The Japanese trainees were tutored by experts and reportedly completed less than half of their initial procedures. A more "real-life" elaboration of the

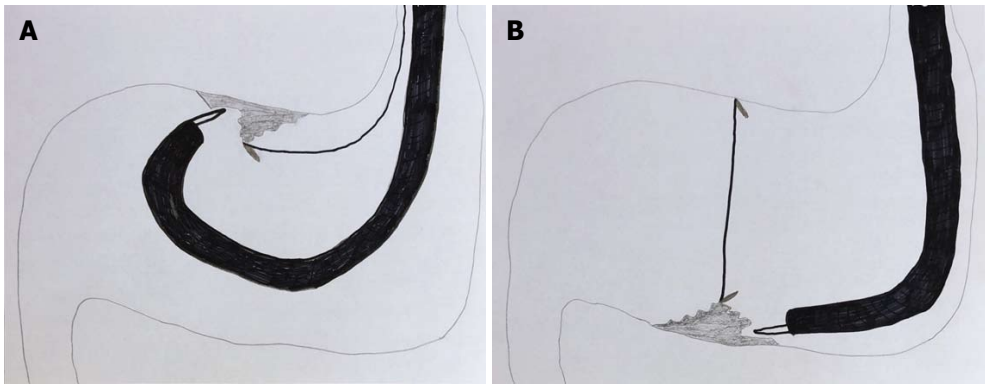

Figure 7 Traction in endoscopic submucosal dissection. A: Traction *via* clip on string; B: Traction *via* pulley effect with two clips.

initial ESD French experience noted 11% and 18% hemorrhage and perforation rate respectively with *en-bloc* and R_0 resection rates of 77%/73% respectively[60]. Berr[51] had suggestions for the "colon heavy-untutored/prevalence based" ESD learners based on his retrospective video analysis of his own work including avoiding: (1) wide SM injection around the lesion (which forces a "perpendicular" instead of "tangential approach"); (2) injection deep to muscle layer (lack of submucosal fluid cushion); (3) disruption of vessels leading to hematoma and loss of transparency of submucosa; (4) dissection without direct vision of the tip of the knife; (5) contact coagulation of small vessel directly on colonic proper muscle layer; and (6) mucosal incision using knife in "pullback fashion" across a haustral fold[51].

Another peril of over-extrapolating ESD results from Japan to the West concerns pathology. One should be cautious concerning extended Japanese indications for gastric ESD (particularly SM1 invasion) (Table 4). The local pathologist may not be as accurate and experienced as expert Japanese pathologists (all SM1 invasion is not created equal (extensive *vs* focal, tumor budding, *etc*.) As reviewed, some surgical studies purport to show that early gastric cancer in the West may behave more aggressively[23,24]. One must discuss risk of metastatic cancer (even after "curative ESD") and metachronous cancers and need for surveillance as even intramucosal carcinoma has a low but not negligible rate of metastasis (*e.g*., 1%-2% for Barrett's intramucosal carcinoma or HGD[61]). The recurrence rate of T1b carcinoma in the rectum (4.2%-4.5%) is higher than in the colon (1.5%-1.9%)[4-6]. Follow-up colonoscopy as well as periodic CEA, abdominal ultrasonography, and thoracic and abdominal CT should be performed. However, no clear consensus was reached regarding the particular method and time of surveillance[62]. Metachronous lesions occur in 10%-30% in early 3-5 years follow-up post gastric, esophageal, colon resection[4,5]. Endoscopic surveillance is important.

Rectal ESD

Rectal ESD merits specific mention as it is in fierce competition with burgeoning techniques of trans-anal surgery including trans-anal endoscopic microsurgery (TEMS), trans-anal minimally invasive surgery (TAMIS) and a host of other platforms. Surgeons have the apparent advantage of better and innovative equipment including robotic devices as surgical resection *via* endoscopy is a natural extension for this discipline. A provocative meta-analysis compared ESD and TEM for rectal lesions demonstrated a relative procedure time, *en-bloc* resection rates, R_0 resection rates, recurrence rates for ESD/TEM of 96/67 min, 88%/99%, 75%/88%, 2.6%/5.2% respectively[63]. The overall complication and emergency surgery rates were about the same (8%, 1.5%). The ESD group had a perforation/hemorrhage rate of 3.7%3.5%, but the surgery group had the more troubling and durable complications of suture leak and fistula (3.2%/0.5%). The surgery group had the distinct advantage in terms of less needed abdominal surgery for oncologic indications or recurrence (8.4% *vs* 2.9%). However, closer scrutiny determines that the ESD group had much more advanced pathology with almost 90% of pathology showing cancer *vs* 10% in the TEM group. Thus, rectal ESD is currently holding its own against these innovative surgical procedures.

Traction

The ESD operator should be aware of gravity during the performance of the section in terms of endogenous fluid and expected blood with consideration of patient repositioning. A practical way to facilitate resection is to employ traction (Figure 7). Traction is the equivalent of a second operator and examples in ESD ranges from simply having a forceps or snare outside the scope channel to setups employing endo-clips, endo-loops, suture thread or floss to create spring or pulley effect. More sophisticated methods employ a second scope, percutaneous access or magnets[64]. Traction may improve performance; especially in trainees and those with modest experience[65].

ESD technology

As mentioned, acquiring skills in ESD is a gateway to innovative resection methods such as STER and EFTR.

Technological innovations are inevitable with many past and future innovations coming from the West. Some of these innovations will make it easier for physicians with a background in EMR to begin ESD, while others will allow experienced ESD operators to perform more challenging cases and to do so more quickly. The already crowded arena of electrosurgical devices and injection solutions will expand. Novel scissors-type knives were invented to facilitate ESD and increase trainee completion rates[66,67]. There is an array of devices being developed as adjuncts to ESD performance. This includes platform devices to allow a variety of instruments to be used synergistically similar to the operating room setup[68]. Balloon devices can allow stabilization of the colonoscope during ESD, and this includes the traditional double balloon endoscope and the DiLumen device (expressively developed for ESD)[69]. Thullim laser is an alternative to the electrosurgical knives powered by monopolar electrosurgical units[70].

CONCLUSION

ESD originated in Japan and is a well-accepted modality in Asia for larger and advanced epithelial-derived neoplasms of the upper and lower gastrointestinal tract. In the West, there is evident interest in ESD as demonstrated by the content of the main gastroenterology and endoscopy journals and national meetings of the related societies. However, ESD has clearly not become part of mainstream endoscopy practice. This is due to multiple factors including the relatively steep learning curve, relative lack of resources for learning ESD including few potential mentors, cost issues, longer procedural time and concern for complications. In addition, societal thought leaders have generally not supported ESD development. Despite this, the consensus (even in the West) is that ESD is the premier modality for resection of EGC and squamous cell esophageal cancer with the exception of small non-advanced lesions. ESD has a more modest niche for Barrett's lesions compared to EMR and surgery though this is still debated. A prime obstacle to ESD implementation in the West is the relative lack of early gastric cancer compared to Asia. The irony is that there is ample colorectal pathology in the West amenable to ESD, but this colon ESD implementation is discouraged by the thought leaders; perhaps because of the relative success of wide-field EMR and the usual relative indolent nature of colon adenoma recurrence. Nonetheless, ESD has clear advantages in the colon and elsewhere in terms of superior *en-bloc* and curative resection rates with associated low recurrence rates. Some ESD "pioneers" have essentially self-tutored themselves in ESD with the more prevalent colorectal lesions. Those embarking on an ESD program should do appropriate preparatory work and avail themselves of international mentors and animal labs before doing clinical work as their resection results and complications will be closely scrutinized. They should also be conservative initially with their choice of potential lesions-especially in the stomach- as there may be biological differences in EGC between the West and the East. We feel that it is inevitable that ESD will eventually be ingrained in mainstream endoscopy practice in the West. This will occur as a result of burgeoning ESD data from the West supporting its validity and utility in this population as well as more potential ESD tutors and perhaps formal society-sanctioned traineeships. The growing demand for basic and adjunctive ESD equipment will spur new devices likely largely derived from the West.

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P- Reviewer: Akiho H, Eleftheriadis NP, Kim GHH **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 239-249

DOI: 10.4253/wjge.v10.i10.239

ISSN 1948-5190 (online)

REVIEW

Artificial intelligence in gastrointestinal endoscopy: The future is almost here

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Author contributions: Alagappan M and Glissen Brown JR contributed equally to this work, and are therefore listed as co-first authors; all authors contributed to this paper with conception, literature review, drafting, editing, and approval of the final version.

Conflict-of-interest statement: Dr. Tyler Berzin is Consultant for Boston Scientific and Medtronic; and Dr. Yuichi Mori is speaking honorarium from Olympus Corp. No other conflict of interest to declare.

Manuscript source: Invited manuscript

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Received: May 10, 2018
Peer-review started: May 10, 2018
First decision: June 6, 2018
Revised: June 9, 2018
Accepted: June 30, 2018
Article in press: June 30, 2018
Published online: October 16, 2018

Abstract

Artificial intelligence (AI) enables machines to provide unparalleled value in a myriad of industries and applications. In recent years, researchers have harnessed artificial intelligence to analyze large-volume, unstructured medical data and perform clinical tasks, such as the identification of diabetic retinopathy or the diagnosis of cutaneous malignancies. Applications of artificial intelligence techniques, specifically machine learning and more recently deep learning, are beginning to emerge in gastrointestinal endoscopy. The most promising of these efforts have been in computer-aided detection and computer-aided diagnosis of colorectal polyps, with recent systems demonstrating high sensitivity and accuracy even when compared to expert human endoscopists. AI has also been utilized to identify gastrointestinal bleeding, to detect areas of inflammation, and even to diagnose certain gastrointestinal infections. Future work in the field should concentrate on creating seamless integration of AI systems with current endoscopy platforms and electronic medical records, developing training modules to teach clinicians how to use AI tools, and determining the best means for regulation and approval of new AI technology.

Key words: Artificial intelligence; Machine learning; Gastrointestinal endoscopy; Computer-assisted decision making; Computer-aided detection; Colonic polyps; Colonoscopy; Computer-aided diagnosis; Colorectal adenocarcinoma

Core tip: Artificial intelligence (AI) appears poised to transform several industries, including clinical medicine. Recent advances in AI technology, namely the improvement in computational power and advent of deep learning, will lead to the near-term availability of clinically relevant applications in gastrointestinal endoscopy, such as real-time, high-accuracy colon polyp detection and classification and fast, automatic processing of wireless capsule endoscopy images. Applications of AI toward gastrointestinal endoscopy will likely exponentially rise in the coming years, and attention should be paid toward regulation, approval, and effective implementation of this powerful technology.

Alagappan M, Glissen Brown JR, Mori Y, Berzin TM. Artificial intelligence in gastrointestinal endoscopy: The future is almost here. *World J Gastrointest Endosc* 2018; 10(10): 239-249 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/239.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.239

INTRODUCTION

Artificial intelligence (AI) has transformed information technology by unlocking large-scale, data-driven solutions to what once were time intensive problems. Over the past few decades, researchers have successfully demonstrated how AI can improve our ability to perform medical tasks, ranging from the identification of diabetic retinopathy to the diagnosis of cutaneous malignancies[1,2]. As the medical community's understanding and acceptance of AI grows, so too does our imagination of the many ways in which it can improve patient care, expedite clinical processes, and relieve the burden of medical professionals.

Gastroenterology is a field that requires physicians to perform a myriad of clinical skills, ranging from dexterous manipulation and navigation of endoscopic devices and visual identification and classification of disease to data-driven clinical decision-making. In recent years, AI tools have been designed to help physicians in performing these tasks. Research groups have shown how deep learning can assist with a variety of skills from colonic polyp detection to analysis of wireless capsule endoscopy (WCE) images[3,4]. As the number of applications of AI in gastroenterology expands, it is important to understand the extent of our success and the hurdles that lie ahead. In this review, we aim to (1) provide a brief overview of artificial intelligence technology; (2) describe the ways in which AI has been applied to gastroenterology thus far; (3) discuss what value AI offers to this field; and finally (4) comment on future directions of this technology.

ARTIFICIAL INTELLIGENCE TECHNOLOGY

Artificial intelligence is machine intelligence that mimics human cognitive function[5]. Research in AI began in the 1950s with the earliest applications being in board games, logical reasoning, and simple algebra. Interest in the field grew over the next few decades due to the exponential increase in computational power and data volume.

Machine learning is an artificial intelligence technique in which computers use data to improve their performance in a task without explicit instruction[6]. Examples of machine learning include an application that learns to identify and discard spam emails or a thermostat that learns household temperature preferences over time. Machine learning is often classified into two categories - supervised and unsupervised learning. In supervised learning, a machine is trained with data that contain pairs of inputs and outputs[7]. The machine learns a function to map the inputs to outputs, which can then be applied toward new examples. Linear and logistic regression, which are often employed in clinical research, are examples of supervised machine learning because they produce a regression function that correlates inputs to outputs based on observed data. In unsupervised learning, machines are given data inputs that are not explicitly paired to labels or outputs[7]. The machine is tasked with finding its own structure and patterns from the set of objects. An example of unsupervised learning is clustering, in which a system creates clusters of similar data points from a large data set.

Feature learning refers to a set of techniques within machine learning that asks machines to automatically identify features within raw data as opposed to the features being explicitly labeled[8]. This technique enables machines to learn features and infer functions between inputs and outputs without being provided the features in advance. A subset of feature learning is deep learning, which harnesses neural networks modeled after the biological nervous system of animals. Deep learning is especially valuable in clinical medicine because medical data often consist of unstructured text, images, and videos that are not easily processed into explicit features.

Machine learning, and more specifically deep learning, has been widely applied in tasks such as gaming, weather, security, and media. Recent notable examples include AlphaGo beating the world's premier Go player, facial recognition within iPhone images, and automatic text generation[9-11].

Deep learning has also shown significant promise in performing clinical tasks. Researchers from Stanford trained a deep convolutional neural network (CNN) on 129450 skin lesion images consisting of 2032 different diseases, and showed that the network performed on par against 21 board-certified dermatologists in distinguishing keratinocyte carcinomas from benign seborrheic keratosis and malignant melanomas from

benign nevi[2]. Other research groups have applied machine learning to identify diabetic retinopathy from fundus photographs, classify proliferative breast lesions as benign or malignant, and predict clinical orders[12-14].

APPLICATIONS OF AI IN GASTROENTEROLOGY

Automatic colonic polyp detection

Automatic colon polyp detection has been one of the primary areas of interest for applications of artificial intelligence in gastrointestinal endoscopy. Generally speaking, automatic polyp detection constructs are designed to alert the endoscopist to the presence of a polyp on the screen through either a digital visual marker or sound.

Numerous studies have demonstrated that endoscopists with higher adenoma detection rates during screening colonoscopy more effectively protect their patients from subsequent risk of colonic cancer[15,16]. Corley *et al*[15], for example, in their evaluation of 314872 colonoscopies performed by 136 gastroenterologists showed that every 1.0% increase in adenoma detection rate was associated with a 3.0% decrease in the risk of cancer (hazard ratio, 0.97; 95%CI: 0.96 to 0.98). However, adenoma miss rates during screening colonoscopy remain relatively high, and have been estimated to be anywhere from 6%-27%[17]. Reasons for missing polyps are myriad, and can include inadequate mucosal inspection (for instance behind folds in the right colon), lack of recognition of subtle mucosal findings representing flat polyps, and variable prep quality. Importantly, there is evidence that some missed polyps are actually present on the visual field, but are not recognized by the endoscopist[18-20].

In the past two decades, several computer-aided detection (CADe) techniques have been proposed to assist endoscopists in the detection of polyps that would otherwise have been missed[21-24]. The ideal automatic polyp detection tool must have (1) high sensitivity for detection of polyps; (2) decreased rate of false positives; and (3) low latency so that polyps can be tracked and identified in near-real time. This last objective has eluded researchers up until recently as automatic polyp detection during live or recorded video can be affected by camera motion, strong light reflections, lack of focus of the traditionally used wide-angle lens, variation in polyp size, location and morphology, and the presence of vascular patterns, bubbles, fecal material and other distractors that may serve as false positives[25].

CADe in optical colonoscopy was first utilized and validated using still images obtained from endoscopic videos. Most of the modalities described below all utilize some combination of the following techniques: pre-processing of an image or series of images in order to discard noise, a feature extraction tool that identifies and extracts a feature or mix of features within the image (*e.g.*, texture, shape or color), and a machine-learning or deep learning classification that uses these features to identify polyps[25].

A number of methods for CADe were proposed in the 1990s. Early attempts included the use of region-growing methods - a pixel-based image segmentation approach - for the extraction of large intestinal lumen contours and for the detection of lower gastrointestinal tract pathology[21-23]. By the end of the 1990s, research efforts mostly combined texture, color, or mixed analysis methods with intelligent pattern classification to aid in the detection of lesions in static endoscopic images[23]. These efforts included work targeting both microscopic features and macroscopic characteristics of lesions within the colon in order to predict the likelihood of neoplastic and pre-neoplastic lesions[26,27]. The concurrent development of neural networks helped push the field forward. Early grey-level texture analysis of endoscopic images included utilization of texture spectrum[24], co-occurrence matrices[28,29], Local Binary Pattern (LBP)[30], and wavelet-domain co-occurrence matrix features[31]. Using this last approach, Karkanis *et al*[31] developed one of the earliest examples of polyp detection software. Known as CoLD (Colorectal Lesions Detector), the software utilized second-order statistical features, calculated on the wavelet transformation of each image to discriminate amongst regions of normal or abnormal tissue. An artificial neural network performed the classification of these features, obtained from still images alone, and the work achieved a detection accuracy of more than 95%[32,33].

Other groups developed methods that utilized color features. Tjoa and Krishnan[34] combined texture spectrum and color histogram features to broadly analyze colon status as "normal" or "abnormal". In 2003, Karkanis *et al*[35] used a color feature extraction scheme built on wavelet decomposition (Color Wavelet Covariance or CWC) to develop a computer-aided detection method with a higher sensitivity than previous methods that were built on grey-level features or color-texture inputs. The CWC method demonstrated a 90% sensitivity and 97% specificity for polyp detection when utilized on high-resolution endoscopy video-frames[35]. In 2015, Zheng *et al*[36] created an intelligent clinical decision support tool that utilized a Bayesian fusion scheme combining color, texture and luminal contour information for the detection of bleeding lesions and luminal irregularities in endoscopic images. In 2006, Iakovidis *et al*[23] developed a pattern recognition framework that accepted standard low-resolution video input and achieved a detection accuracy of greater than 94.5%.

These early works were based on the analysis of static endoscopic images and video frames. Subsequent work focused on translating polyp detection methods to real-time video analysis. In 2016, Tajbakhsh *et al*[37] developed a CADe system that used a hybrid context-shape approach, whereby context information was used to remove non-polypoid structures from analysis

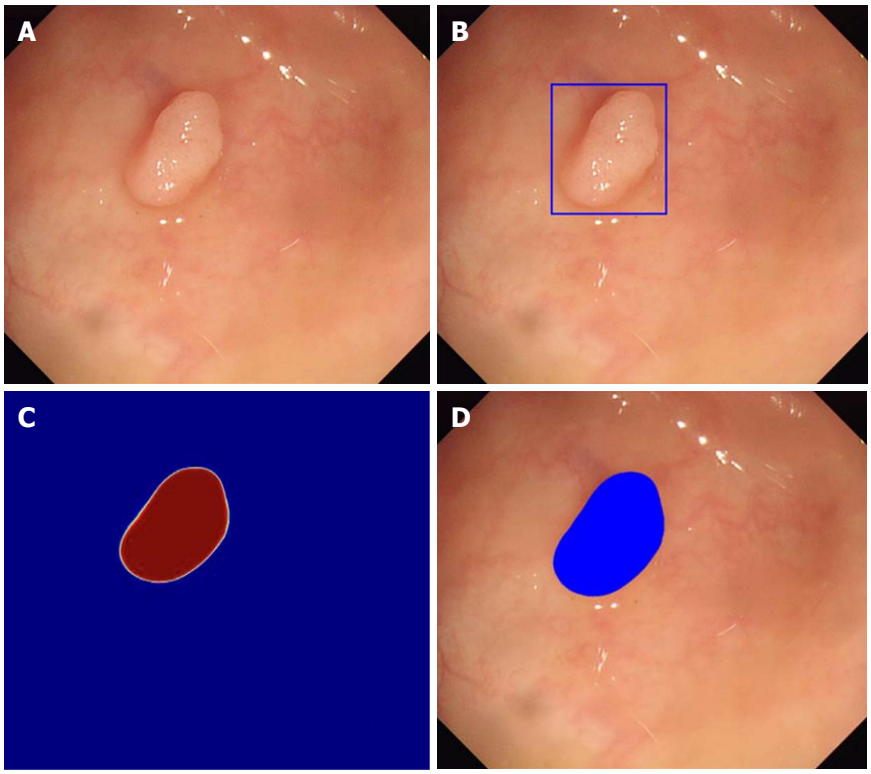

Figure 1 Automatic polyp detection by Wang *et al*[40]. A: Original image obtained during colonoscopy; B: Automatic detection by box method; C: Probability map whereby red indicates high probability of polyp and blue indicates low probability of polyp; D: Automatic detection by paint method whereby blue coloring indicates location of polyp.

and shape information was used to localize polyps. Using this system, Tajbakhsh *et al*[37] reported an 88% sensitivity for real-time polyp detection. Perhaps more importantly, this group showed a latency, defined as the time from the first appearance of a polyp in the video to the time of its first detection by the software system, of only 0.3 s. The limitation to this study was its retrospective nature and limited clinical generalizability, as the system was tested on only twenty-five unique polyps[37].

Subsequent work in optical colonoscopy focused on validating real-time polyp detection modalities on larger colonoscopy image databases. Fernández-Esparrach *et al*[38] developed a method for utilizing energy maps based on localization of polyps and their boundaries - a so-called Window Median Depth of Valleys Accumulation (WM-DOVA) energy map method. Using this method on 24 videos containing 31 different polyps, this group demonstrated a sensitivity of 70.4% and a specificity of 72.4% for detection of polyps[38]. Wang *et al*[25] developed a method that utilized edge-cross section visual features and a rule-based classification to detect "polyp edges". This Polyp-Alert software was trained on 8 full colonoscopy videos and subsequently tested on 53 randomly selected full videos. The system correctly detected 42 of 43 (97.7%) polyps on the screen and did so with very little latency. However, the software had an average of 36 false-positives per colonoscopy video analyzed[25]. False positives commonly resulted from protruding folds, the appendiceal orifice and ileocecal valve, and areas of the colon with residual fluid[25].

Both of these approaches were based on traditional machine learning methods with explicit feature specification. More recently, several groups have begun to incorporate deep learning methods into CAD systems. At Digestive Disease Week 2016, Li *et al*[39] presented perhaps the first example of a deep learning system for polyp detection. This group trained a convolutional neural network on 32305 colonoscopy images, and achieved an accuracy of 86% and sensitivity of 73% for polyp detection[39]. This study was instrumental in showing that a deep learning based computer vision program could accurately identify the presence of colorectal adenomas from colonoscopic images. Wang *et al*[40] recently presented their deep learning polyp detection software at the 2017 meeting of the World College of Gastroenterology. This system, built on a SegNet Architecture system was developed using a retrospective set of 5545 endoscopist-annotated images from colonoscopies performed in China and subsequently validated prospectively using 27461 colonoscopy images from 1235 patients (Figure 1)[40]. It is currently being testing in a single-center prospective feasibility study[40]. More recently, Misawa *et al*[41] developed a deep learning based AI system, which was trained on 105 polyp-positive and 306 polyp-negative videos. The system was tested on a separate data set, and was able to detect 94% of polyps with a false positive detection rate of 60%[41].

Deep learning methods hold the promise of increasing

diagnostic accuracy and processing large amounts of data quickly. Future work must continue to develop methods that balance a high sensitivity with low latency and improved false positive rates.

Optical biopsy

Once a lesion has been detected, computational analysis may help predict polyp histology without the need for tissue biopsy, a subfield sometimes referred to as computer-aided diagnosis (CADx). The field of optical biopsy is several decades old, but the addition of deep learning and the increasing complexity of computational analytic methods have led to recent developments in this field. The ability to diagnose small polyps such as diminutive adenomas in-situ *via* optical diagnosis may allow for adenomas to be resected and discarded rather than sent for sometimes unnecessary histopathologic examination[42]. This "resect and discard" strategy has been estimated to promise upwards of $33 million dollars in savings per year in the United States alone[43]. A similar "diagnose and disregard" strategy has been suggested for diminutive polyps such as hyperplastic polyps in the rectosigmoid colon, where non-neoplastic polyps are identified *via* optical biopsy and left in place.

Historically, advanced imaging modalities have been the main areas of investigation for optical biopsy. These include chromoendoscopy, narrow spectra technologies (Narrow Band Imaging, i-Scan, and Fujinon intelligent color enhancement), endocytoscopy, and laser-induced fluorescence spectroscopy. In Japan, chromoendoscopy, defined as the topical application of stains or pigments to improve tissue localization during endoscopy, is widely used to further characterize small polyps during standard screening and surveillance colonoscopy[44]. The Kudo pit-pattern is one of the most widely known classification systems used to classify and predict the histopathology of a given lesion[27]. Takayama *et al*[45] found that chromoendoscopy combined with magnifying endoscopy (in this case an endoscope that magnified images by a factor of 40) achieved a sensitivity for the diagnosis of dysplastic crypt foci of 100%.

Narrow band imaging (NBI) is another endoscopic optical modality where blue and green light is used to enhance the mucosal detail of a polyp in order to better characterize vessel size and pattern[46]. The NBI International Colorectal Endoscopic (NICE) classification uses color, vessels and surface pattern to differentiate between hyperplastic and adenomatous histology[47]. However, NBI, like chromoendoscopy, has been shown to have significant interobserver and intraobserver variability[48,49]. Interobserver variance generally stems from differences in expertise, while intraobserver variance is affected by experience, personal well-being, levels of distraction, and stress[50].

The existence of inter- and intraobserver variance and steep learning curves have likely contributed to the slow pace of adoption of these techniques beyond specialized medical centers. The use of CADx modalities may allow for decreased variance amongst providers, increased standardization, and, perhaps most importantly, more widespread adoption by non-experts in the field[51]. Following a similar developmental trajectory as the field of automatic polyp detection (CADe), the first CADx systems were developed using static colonoscopic images and image series. In 2010, Tischendorf *et al*[50] developed a computer-based analysis algorithm for colorectal polyps using magnifying NBI, with a subsequent automatic classification scheme using machine learning. This system achieved a sensitivity of 90% compared to a human sensitivity of 93.8% when using the same database of 209 polyp images (with corresponding biopsy)[50]. In a follow up study on smaller polyps in 2011, Gross *et al*[52] reported a 95% sensitivity in the computer based-algorithm group compared to a 93.4% sensitivity in a human expert group and 86.0% sensitivity in a human non-expert group. Both of these studies were limited, however, in that they involved off-site computer analysis of static images.

Subsequent work by Takemura *et al*[53] and Kominami *et al*[54] translated machine learning methods to real-time clinical use. Takemura *et al*[53] developed a custom software (HuPAS version 3.1, Hiroshima University, Hiroshima, Japan) that utilized a "bag-of-features" representation of NBI images and hierarchical k-means clustering of local features. In an initial study using static images, this group showed a sensitivity of 97.8%, specificity of 97.9%, and accuracy of 97.8% for diagnosis of neoplastic lesions. Diagnostic concordance between the computer-aided classification system and the two experienced endoscopists was 98.7%[53]. In a follow up study, this same group developed a real-time software to automatically recognize polyps, and then analyze and classify them as neoplastic or non-neoplastic[54]. This approach yielded a sensitivity 93.0%, a specificity of 93.3%, accuracy of 93.2%, and concordance between the image recognition software and human endoscopic diagnosis of 97.5%[54]. Though this was a study on just 41 patients with 118 colorectal lesions, it was the first of its kind to demonstrate that CADx in real-time is feasible and comparable to human diagnostics using magnified NBI.

Several other advanced endoscopy imaging modalities have similarly benefited from advances in CAD. Endocytoscopy (EC) is an ultra-high magnification technique that provides images of surface epithelial structures at cellular resolution[55]. In 2015, Mori *et al*[56] developed the EC-CAD system, a machine-learning CAD system that uses nuclear segmentation and feature extraction to predict pathologic classification (*i.e.*, non-neoplastic, adenoma and cancer, unable to diagnose). In a pilot study consisting of images from 176 polyps and 152 patients, the system showed a sensitivity of 92.0% and specificity of 79.5% compared to a sensitivity of 92.7% and specificity of 91% by expert endoscopists[56]. Misawa *et al*[57] then developed an EC system that utilized NBI rather than dye staining, and developed

Table 1 Summary of clinical studies involving computer-aided detection and computer-aided diagnosis in real time (during live colonoscopy or video recording)

Reference	Year	Type of CAD	Endoscopic Modality/ Input	Processing Modality	Study Design	Sensitivity	Specificity	Accuracy	Latency	Notes
Wang *et al*[25]	2015	CADe	White-Light Endoscopy	Polyp-Edge Detection Algorithm and Shot Extraction	Retrospective	-	-	97.7%[1]	0.02 s	36 false-positives per video
Fernández-Esparrach *et al*[38]	2016	CADe	White-Light Endoscopy	WM-DOVA	Retrospective	70.4%[2]	72.4%[2]	-	-	Accuracy and latency reported for this study
Tajbakhsh *et al*[37]	2016	CADe	White-Light Endoscopy	Hybrid Context-Shape Extractor, Edge Mapping	Retrospective	88.0%[2] for CVC-ColonDB 48.0% for ASU-Mayo	-	-	0.3 s	0.1 False positives per frame
Wang *et al*[40]	2017	CADe	White-Light Endoscopy	Deep learning, built on SegNet Architecture	Retrospective	91.6%[2]	96.3%[2]	100.0%[1]	0.04 s	
Misawa *et al*[41]	2018	CADe	White-Light Endoscopy	Deep learning, built on a DCNN	Retrospective	90.0%[2]	63.3%[2]	76.5%[1]	-	
Kominami *et al*[54]	2016	CADx	Magnifying NBI	Bag of features representation, SVM output	Prospective	93.0%[3]	93.3%[3]	93.2%[4]	-	97.5% concordance between automatic diagnosis and endoscopic diagnosis
Komeda *et al*[75]	2017	CADx	A mix of White-Light Endoscopy, NBI and Chromoendoscopy	Deep learning, built on a CNN	Retrospective	-	-	75.1%[5]		
Byrne *et al*[59]	2017	CADx	White-Light Endoscopy and NBI	Deep learning, built on a DCNN	Retrospective	98.0%[3,6]	83.0% [3,6]	94.0%[4]	0.05 s	For 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%
Mori *et al*[58]	2017	CADx	Endocytoscopy and NBI	Texture analysis, automatic vessel extraction, SVM output	Prospective	97.0%[3]	67.0%[3]	83.0%[4]		

[1]Tracking accuracy or detection rate, defined as number of polyps detected by software/total number of polyps present in videos; [2]Sensitivity and specificity for the detection of polyps; [3]Sensitivity and specificity for the diagnosis of neoplastic versus non-neoplastic lesions; [4]Accuracy defined as differentiation of adenomas from non-neoplastic lesions; [5]Accuracy of a 10-hold cross-validation is 0.751, where the accuracy is the ratio of the number of correct answers over the number of all the answers produced by the CNN; [6]Sensitivity and specificity in this case are calculated based on histology of 106/125 polyps in the video test set. For the remaining 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%; CADx: Computer-aided diagnosis; CADe: Computer-aided detection; SVM: Support vector machine; WM-DOVA: Window median depth of valleys accumulation; NBI: Narrow band imaging; CNN: Convolution neural network; DCNN: Deep convolution neural network.

a machine learning CAD system referred to as AI-assisted endocytoscopy to analyze EC-NBI images produced by this instrument. This system uses texture analysis and automatic vessel extraction, which is analyzed by a support vector machine and outputs a 2-class diagnosis (non-neoplastic or neoplastic) in real time with a 0.3 second latency[57]. In a recent validation study using 100 randomly selected images of colorectal lesions, the AI-assisted endocytoscopy achieved a sensitivity of 85% for the diagnosis of adenomatous polyps, a specificity of 98%, and an accuracy of 90% (Figure 2)[57]. Mori *et al*[58] recently reported on the results of a prospective study further studying the AI-assisted endocytoscopy system. This single-center study in Yokohama, Japan involved 88 men and women with 126 polyps. The system demonstrated a sensitivity of 97%, specificity of 67%, accuracy of 83%, and positive and negative predictive values of 78% and 95% with extremely low latency.

With the advent of deep learning, real-time optical analysis of polyps may be possible using white-light alone, without the aid of advanced, endoscopic imaging modalities such as chromoendoscopy, NBI, endocytoscopy or laser-induced autofluorescence spectroscopy (Table 1). In 2017, Byrne *et al*[59] developed and trained an AI deep convolution neural network (DCNN) on both unaltered white-light and NBI colonoscopy video recordings (Figure 3). The network was tested on 125 videos of consecutively encountered diminutive polyps, and achieved a 94% accuracy of classification for 106 of the 125 videos (for 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%). For these 106 polyp videos, the system was able to detect adenomas with a sensitivity of 98% and a specificity of 83%[59]. Furthermore, the model worked in quasi

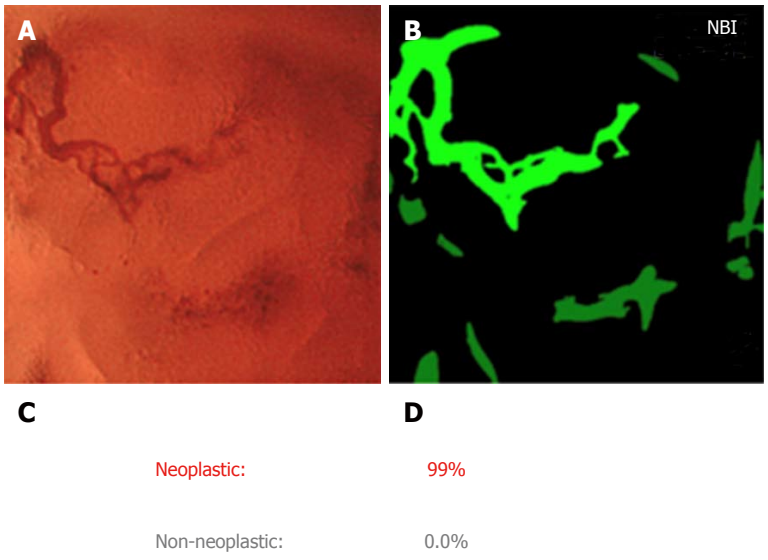

Figure 2 Output from artifical intelligence-assisted endocytoscopy system by Misawa *et al*[57]. A: Input from endocytoscopy with narrow band imaging; B: Extracted vessel image whereby green light represents extracted vessel image; C: System outputs diagnosis of neoplastic or non-neoplastic; D: Probability of diagnosis calculated by support vector machine classifier. NBI: narrow band imaging.

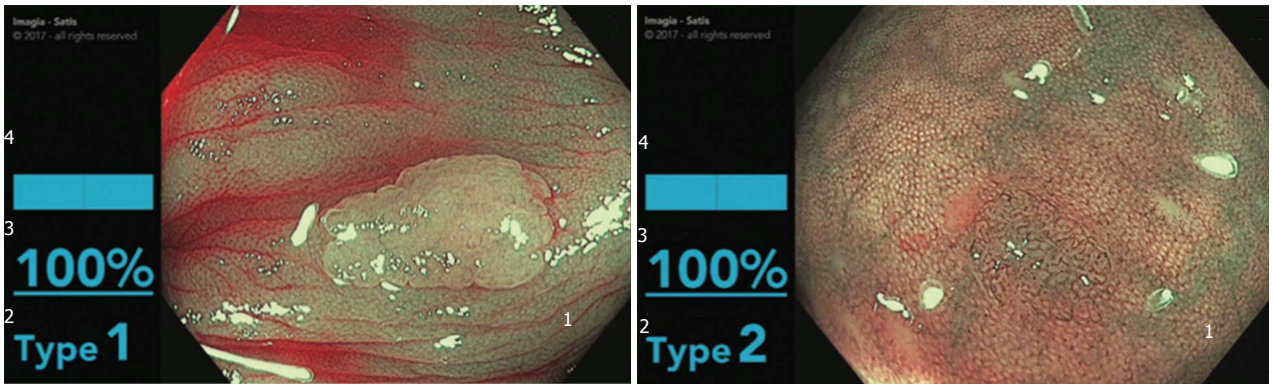

Figure 3 Automatic polyp classification system. 1: Input from narrow band imaging; 2: Computer diagnosis of NICE type 1 (hyperplastic) *vs* NICE type 2 (adenomatous); 3: Probability of diagnosis; 4: Computer determined confidence in diagnosis probability. Obtained with permission from Dr. Michael Byrne (Division of Gastroenterology at Vancouver General Hospital and UBC).

real-time with a delay of just 50ms per frame[59]. This work is also significant in that it achieved the diagnostic thresholds set forth by the Preservation and Incorporation of Valuable Endoscopic Innovations initiative set forth by the American Society for Gastrointestinal Endoscopy. This initiative states that in order for optical biopsy to reach an acceptable threshold to support the "resect and discard" or "diagnose and leave strategies", there must be ⩾ 90 % agreement for post-polypectomy surveillance intervals for the "resect and discard" strategy, and ⩾ 90% negative predictive value (NPV) for adenomatous histology for the "diagnose and leave" strategy[60].

Future work in this field must by necessity continue to refine sensitivity, specificity, accuracy, PPV and NPV of real-time optical classification methods while working to combine CADe and CADx modalities.

EGD and capsule endoscopy

Compared to applications in colonic polyp detection and classification, there have been fewer applications of deep learning in other areas of gastroenterology. However, the existing applications deserve recognition for their novelty and promise. One notable application is the use of CNN to diagnose *Helicobacter pylori* (*H. pylori*) infection by analysis of gastrointestinal endoscopy images[61]. *H. pylori* is strongly linked to gastritis, gastroduodenal ulcers, and gastric cancer, so prompt and effective diagnosis and eradication of this infection is important[62]. Existing diagnostic methods for *H. pylori* infection including urea breath test and stool antibody testing are highly sensitive and specific, but can be logistically difficult to schedule and process. In this study by Itoh *et al*[61], researchers developed a CNN trained on 149 gastrointestinal endoscopy images and tested on 30 images. The resulting sensitivity and specificity of the CNN for detection of *H. pylori* infection was 86.7% and 86.7% with an AUC of 0.956, which is significantly better than the performance of human

endoscopists[61,63].

Deep learning with convolutional neural networks has also been applied toward endoscopic detection of gastric cancer. In 2018, Hirasawa *et al*[64] constructed a CNN-based diagnostic system which was trained on more than 13000 endoscopic images of gastric cancer. The system was then tested on 2296 images and in just 47 s, correctly diagnosed 71 of 79 gastric cancer lesions for a sensitivity of 92.2%. However, the positive predictive value was only 30.6% as a result of several false positives. This study highlights the potential of deep learning systems to accurately and quickly detect cancer. One can expect that with more training data and improved computational hardware, both the accuracy and analysis speed will only improve.

Several studies have demonstrated applications of deep learning in wireless capsule endoscopy (WCE). A major challenge of WCE for busy clinicians is the time-intensive nature of reviewing the images. However, deep learning offers a solution to both problems - it provides quick analysis of large-volume data and uses representation learning to extract its own features from unstructured images. Capsule endoscopy can be used to identify mucosal changes characteristic of celiac disease, but visual diagnosis has low sensitivity[65]. Zhou *et al*[66] trained a CNN using capsule endoscopy clips from patients with and without celiac disease, and reported a sensitivity and specificity of 100% for distinguishing celiac disease patients from controls in a testing set of ten patients. Further, the study found that the evaluation confidence of the system was correlated to the severity of the small bowel mucosal lesions.

Deep learning in WCE has also been shown to be effective in detection of small bowel bleeding. The first several studies to demonstrate computer-aided diagnosis of bleeding from WCE images used RGB and color texture feature extraction to help distinguish areas of bleeding from non-bleeding[67-69]. More recent studies, including by Xiao *et al*[70] and Hassan *et al*[71], used deep learning and feature learning to achieve sensitivities and specificities as high as 99% for detection of gastrointestinal (GI) bleeding. Further research and validation of these models may allow for a fast and highly effective means of detecting GI bleeding, with less work for the interpreting physician.

Similar image processing methods have even been applied to infectious disease detection in WCE. He *et al*[72] developed a CNN to detect hookworms, a cause of chronic infection affecting an estimated 740 million people in areas of poverty[72,73]. Hookworm infections cause chronic intestinal blood loss resulting in iron-deficiency anemia and hypoalbuminemia, and are especially dangerous in children and women of reproductive age due to its adverse effects in pregnancy[73]. In this study, He *et al*[72] tested a CNN on 440000 WCE images, and developed a system with high sensitivity and accuracy for hookworm detection. Applications of deep learning to hookworm detection and diagnosis of other infectious disease in the gastrointestinal tract may provide significant clinical value worldwide, especially in low-resource settings, if the cost of capsule endoscopy can be substantially lowered.

VALUE OF AI IN GASTROENTEROLOGY

As seen from the examples of CAD in gastroenterology described above, there are numerous potential benefits to the development and integration of CADx and CADe systems in everyday practice. In general, using artificial intelligence as an adjunct to standard practices within GI has the potential to improve the speed and accuracy of diagnostic testing while aiming to offload human providers from time-intensive tasks. In addition, CAD systems are not subject to some of the pitfalls of human-based diagnosis such as inter- and intraobserver variance and fatigue.

We are entering an age where CAD tools, applied in academic research settings, can at least match, and sometimes exceed human performance for the detection or diagnosis of endoscopic findings in a variety of modalities within gastroenterology[74]. Current prospective studies generally utilize CADe and CADx as a "second reader", where information derived from CAD systems serve to support the endoscopist's diagnosis. When used in this fashion, CAD modalities can assist human providers with time-intensive, data-rich tasks. Several studies have shown that human observation of standard colonoscopy video by either nurses or trainees may increase an individual provider's polyp and adenoma detection rates[18-20]. The CADe systems described above, when integrated into daily practice, may offer a reliable, and ever-vigilant "second observer," which could provide particular value for junior gastroenterologists or endoscopists with low adenoma detection rates[38].

FUTURE DIRECTIONS

As applications of artificial intelligence in gastroenterology continue to increase, there are several areas of interest that we believe will hold significant value in the future. First, the technical integration of artificial intelligence systems with existing electronic medical records (EMR) and endoscopy platforms will be important to optimize clinical workflow. New AI applications must be able to easily "read in" data from a video input or EMR, allowing the systems to use the data for training and real time decision support. A seamless integration in the endoscopy suite will be crucially important in encouraging clinician adoption.

Second, AI systems must continue to expand their library of clinical applications. As discussed in this review, there are several promising studies that demonstrate how AI can improve our performance on clinical tasks such as polyp identification, detection of small bowel bleeding, and even endoscopic recognition of *H. pylori* and hookworm infection. Future research should continue to identify new clinical tasks that are well-suited to machine learning tools. For example, analysis

of WCE for diagnosis of celiac disease suggests that similar methodologies may be effective in diagnosing inflammatory bowel disease or providing more objective scoring of mucosal IBD activity during treatment. From a performance perspective, AI systems in clinical endoscopy will need to eliminate latency in detection to facilitate the real-world applicability of these technologies.

Third, further research is needed to understand the ethical and pragmatic considerations involved in the integration of artificial intelligence tools in gastroenterology practice. To begin, what is the general physician sentiment toward artificial intelligence? Is AI considered a threat or a tool by the gastroenterology community? A deeper understanding of the end-user is crucial to dictating how these tools should be designed and deployed. If AI tools are accepted by physicians, how will we train individuals to use these technologies effectively? Will the learning curve for using these systems be prohibitive? If so, further research is needed to describe the most effective training methods for physician practices beginning to adopt AI technology. In today's technology-driven environment, it is clear that data security is of utmost importance, especially when dealing with protected health information. As the number of AI tools increases, so too should our efforts toward designing security systems and encryption methods to safeguard clinical data. Finally, the clinical community needs to decide on standards for approval and regulation of new AI technologies, including potential implications for legal matters including medical malpractice.

CONCLUSION

Artificial intelligence is an exciting new frontier for clinical gastroenterology. Artificial intelligence techniques like deep learning allow for expedited processing of large-volume unstructured data, and in doing so enable machines to assist clinicians in important tasks, such as polyp detection and classification. Several research groups have shown how artificial intelligence techniques can provide significant clinical value in gastroenterology, and the number of applications will likely continue to expand as computational power and algorithms improve. As the field evolves, a watchful eye is needed to ensure that security, regulation, and ethical standards are upheld.

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P- Reviewer: Poskus T, Shi H, Zhang QS **S- Editor**: Wang JL
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 250-258

DOI: 10.4253/wjge.v10.i10.250

ISSN 1948-5190 (online)

MINIREVIEWS

Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand?

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Author contributions: Galanopoulos M designed the review; Galanopoulos M, Gkeros F, Tsoukali E, Karampekos G and Vraka M analyzed and interpreted the data; Galanopoulos M and Matzaris GJ drafted the manuscript; Matzaris GJ critically revised the paper.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Manuscript source: Invited manuscript

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Received: May 29, 2018
Peer-review started: May 29, 2018
First decision: June 6, 2018
Revised: June 24, 2018
Accepted: June 28, 2018
Article in press: June 29, 2018
Published online: October 16, 2018

Abstract

Patients with long-standing ulcerative colitis (UC) and extensive Crohn's colitis (CC) are at increased risk for dysplasia and colorectal cancer (CRC). Several studies have shown that UC extending proximal to the rectum, CC involving at least 1/3 of the colon, co-existence of primary sclerosing cholangitis, undetermined or unclassified colitis, family history of CRC and young age at diagnosis appear to be independent risk factors for inflammatory bowel disease (IBD) - related CRC. Therefore, screening and surveillance for CRC in IBD patients is highly recommended by international and national guidelines, whilst colonoscopy remains the unequivocal tool in order to detect potentially resectable dysplastic lesions or CRC at an early stage. Although the importance of screening and surveillance is widely proven, there is a controversy regarding the time of the first colonoscopy and the criteria of who should undergo surveillance. In addition, there are different recommendations among scientific societies concerning which endoscopic method is more efficient to detect dysplasia early, as well as the terminology for reporting visible lesions and the management of those lesions. This article concisely presents the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD focusing on their evidence-based accuracy and efficiency, as well as their cost-effectiveness. Finally, newer methods are mentioned, highlighting their applicability in daily endoscopic practice.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Dysplasia; Colorectal cancer;

Endoscopy; Chromoendoscopy; Surveillance

Core tip: There is an established association between inflammatory bowel disease (IBD) and colorectal cancer (CRC). Therefore, surveillance of these patients for CRC is crucial and recommended by international guidelines. In this review we present the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD, highlighting chromoendoscopy with targeted biopsies as the gold standard method. Finally, newer methods are mentioned, examining their applicability in daily endoscopic practice.

Galanopoulos M, Tsoukali E, Gkeros F, Vraka M, Karampekos G, Matzaris GJ. Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand? *World J Gastrointest Endosc* 2018; 10(10): 250-258 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/250.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.250

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a higher incidence of colorectal cancer (CRC) compared to the general population, even though only 1% of all CRC cases are attributed to IBD[1]. The incidence rates reported by Eaden *et al*[2,3], as well as the St. Mark's group in the United Kingdom, showed comparable cumulative probabilities of CRC and dysplasia, approximately 8% and 18% by 20 and 30 years of ongoing disease, respectively. According to Bernstein *et al*[4], both Crohn's disease (CD) and ulcerative colitis (UC) patients face an increased risk for colon cancer [relative risk (RR) 2.64 and 2.75, respectively]. Factors linked to an increased incidence of CRC include: prolonged duration of colitis, extensive colonic involvement, presence of primary sclerosing cholangitis (PSC), positive family history for CRC and, according to some studies, earlier onset and severity of inflammation[1,5-9] (Table 1). Oncogenesis in IBD has been well described as a result of chronic inflammation, leading *via* low- and high-grade dysplasia, finally, to CRC[1,10-24] (Figure 1). Dysplasia is divided into two categories: (1) Endoscopically visible dysplastic lesion, *e.g*., polyps, which are detected by targeted biopsies or resection of endoluminal masses; and (2) Endoscopically invisible dysplasia which is detected by blinded random biopsies on endoscopically normal lumen and is characterized as the most dependable marker for increased CRC risk in IBD patients[1,25,26]. The resection of visible dysplasia, in combination with a rigorous follow-up program has been shown to be a safe alternative to colectomy for select patients[27,28]. On the other hand, a study by Picco *et al*[29] showed that the detection rate for dysplasia with the use of white light endoscopy (WLE) was 9.3%, compared to 21.3% when using both WLE and dye-spray chromoendoscopy (DCE). This demonstrates the need for the implementation of a surveillance strategy in IBD patients based on better techniques and technologies, aiming at reducing the prevalence of metachronous lesions during follow-up. However, uncertainties exist regarding the soundness of this approach on preventing CRC. In a recent systematic review, people undergoing periodic surveillance for CRC were not found to have lower mortality when compared to those under no surveillance (RR 0.81, 95%CI: 0.17 to 3.83)[30,31].

Nevertheless, the current recommendations favor DCE with targeted biopsies of any identified lesions[1,26,32,33] (Figure 2). Whenever DCE is not available, WLE with random, four quadrant biopsies every 10 cm should be performed with additional targeted biopsies from visible lesions. Other endoscopic modalities, like narrow band imaging (NBI), i-SCAN and autofluorescence imaging, did not achieve superior dysplasia detection rates when compared to standard (SD)- or high-definition (HD) WLE in randomized controlled trials[34-39].

Taking all these into consideration, the aim of our review is the brief and up-to-date description of the basic screening endoscopic modalities, as well as their efficacy and accuracy for CRC surveillance in IBD patients.

STANDARD-DEFINITION AND HIGH-DEFINITION WHITE LIGHT ENDOSCOPY

The standard method in CRC surveillance has until recently been SD colonoscopy, with the use of targeted as well as random quadrant biopsies every 10 cm, which amounts to at least 33 biopsies to achieve 90% confidence of detecting dysplasia. However, this technique ultimately inspects less than 1% of the mucosal surface of the colon[40]. According to a Dutch study examining long-standing UC, the overall rate of dysplasia detection with SD colonoscopy was 0.19[36]. With the advent of HD endoscopes and monitors, the endoscopist is able to better identify dysplastic lesions. A study by Subramanian *et al*[41] comparing SD to HD colonoscopy for dysplasia screening in UC, reported a three-fold increase in the yield of the HD endoscope combined with targeted, as well as random biopsies, especially in the right colon. Based on the aforementioned study, the SCENIC consensus statement by American Society for Gastrointestinal Endoscopy (ASGE) favors HD- over SD-WLE when implementing a surveillance program, even though the HD cost remains a limitation[33]. This improvement in detection of dysplastic lesions by HD-WLE and targeted-biopsy sampling changed the therapeutic considerations regarding colectomy, favoring more conservative approaches[41]. Furthermore, it was pointed out that the increased turnout with HD colonoscopy is probably a true reflection of the increased yield of this technique[41]. Nevertheless, based on the same study, neither

Table 1 Colorectal cancer risk factors and surveillance

High risk factors
Annual surveillance
Extensive colonic involvement (pancolitis, CD with > 50% colonic involvement)
Moderate-severe endoscopic or histological active inflammation sustained over time
PSC
Disease commencing at age < 15 yr
Family history of sporadic CRC in a first-degree relative < 50 yr
Presence of a stricture or dysplasia detected during the previous 5 yr
High risk factors in case of pouch existence
Dysplasia
Previous CRC
Type C mucosa
Intermediate risk
Every three years surveillance
Mild or moderate endoscopic/histological inflammation sustained over time
Family history of sporadic CRC in a first-degree relative older than 50 yr
Presence of inflammatory polyps
Low risk factors
Every five years surveillance
Pancolitis without inflammation
Left-sided UC or CD with < 50% colonic involvement

CRC: Colorectal cancer; CD: Crohn's disease; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis.

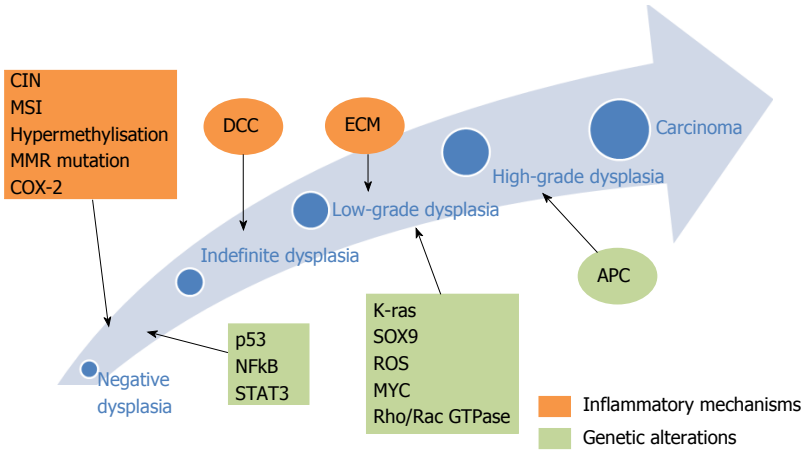

Figure 1 Colitis-associated colon cancer sequelae. COX-2: Cyclooxygenase-2; ECM: Extra-cellular matrix; MMR: Mismatch repair mutation; DCC: Deleted in colorectal carcinoma; APC: Adenomatous polyposis coli; MSI: Microsatellite instability; CIN: Chromosomal instability; ROS: Reactive oxygen species; K-ras: Kirsten rat sarcoma 2 viral oncogene homolog; p53: Tumor protein p53; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3: Signal transducer and activator of transcription 3; *SOX9*: SRY-box 9 gene.

significant change in the detection of lesions with high grade dysplasia nor early carcinoma or flat lesions were observed.

On the contrary, the study by van den Broek *et al*[36] showed no substantial difference in clinical outcomes for patients, in whom low grade dysplasia was revealed using random biopsies, thus advocating the use of improved visualization through advanced techniques[36,41].

Concluding, even though the most widespread technique for dysplasia surveillance in IBD until recently has been the WLE with random biopsies, it is arduous and protracted[40]. Furthermore, the diagnostic reliability of WLE is challenged in a recent review, which found a sensitivity of 76%[42]. Therefore, this method's practicability has been clearly questioned and the research for the development of diagnostic modalities is supported[43].

RANDOM BIOPSIES

Four quadrant biopsies every 10 cm throughout the colon has been the gold standard of IBD surveillance for more than 30 years. This approach originates from the theory of "flat dysplasia", which suggests that dysplasia is difficult to visualize in colitis-affected mucosa[40,44]. Random biopsy only samples less than 1% of the luminal mucosa; has a subpar detection rate (< 2 per 1000 biopsies taken) and when used in conjunction with advanced endoscopic techniques, it does not affect clinical decisions[44]. A large retrospective analysis by van den Broek *et al*[36] reviewing 1010 colonoscopies during 10 years of surveillance stated that the result of random biopsy surveillance was poor, and neoplasia was detected only in four patients with random biopsies.

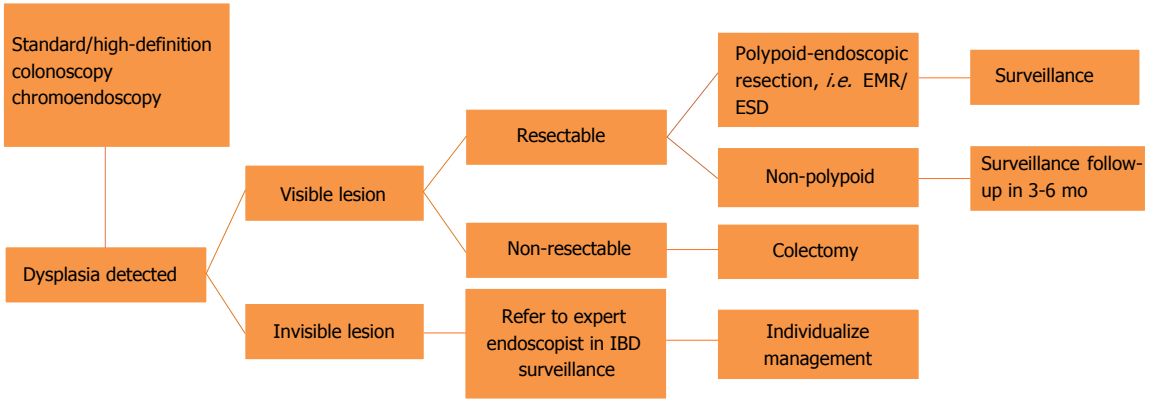

Figure 2 Algorithm for colorectal cancer surveillance in inflammatory bowel disease patients. IBD: Inflammatory bowel disease; EMR:

Additionally, neoplasia was macroscopically visible in 94% of colonoscopies[43,44]. Current guidelines by British Society of Gastroenterology (BSG) and ASGE advocate the use of DCE without the need for random biopsies; however, it is suggested that random biopsies be acquired during HD colonoscopy, if DCE is not available or technically feasible[26]. Random biopsies remain a reasonable alternative if there are conditions that lower the diagnostic yield, such as inflammation, pseudo-polyposis, poor preparation or a poorly visualised mucosa[26,45].

DYE-SPRAY CHROMOENDOSCOPY

Several studies have proven the efficacy of DCE in the detection of dysplasia in patients with IBD. DCE may reduce the need for random biopsies and may allow prolonged surveillance-interval, leading to cost reduction, as well as an increase the detection sensitivity of dysplastic lesions per examination[46].

This technique helps to augment dysplasia detection by topical application of dye on the colonic mucosa during colonoscopy. Areas that are macroscopically elevated or depressed, friable, obscure in vasculature, and with a villous or nodular pattern, can be detected more easily and biopsies can be taken. The most common dyes that in use are methylene blue and indigo carmine[47]. Dye solution can be sprayed by catheter, or flushing pumps, or administered as controlled release tablets, taken with bowel preparation[48]. When performing DCE, it is important to avoid active disease and to have adequate bowel preparation. Paris classification seems to be the standard method to describe any visible lesion, and targeted biopsies should be taken from any suspected area. If the lesion is well-defined, *en-bloc* endoscopic resection should be performed and biopsies should be taken from the adjacent mucosa. In case the lesion is unresectable, the endoscopist should take biopsies and tattoo the area.

Kiesslich *et al*[49] were the pioneers conducting a large randomized study with 263 individuals with long-standing UC. In the DCE-group, there was a statistically important correlation between the endoscopic estimation of the level and extent of inflammation of the colon ($P = 0.0002$) and the histology report, when compared to WLE ($P = 0.0002$) (89% *vs* 52% $P < 0.0001$). Additionally, more targeted biopsies were possible and these biopsies detected significantly more intraepithelial neoplasia (INs) when performing DCE (32 *vs* 10 $P = 0.003$). In a well-designed prospective study, Hurlstone *et al*[50] examined 350 patients with long-standing UC undergoing colonoscopy surveillance with high-magnification chromoscopic colonoscopy (HMCC) comparing the data with matched controls who had undergone WLE. The HMCC-group found significantly more intraepithelial neoplasias compared to controls (69 *vs* 24 $P < 0.0001$), and only 0.16% of the random biopsies have shown INs *vs* 8% from the targeted biopsies. Furthermore, Marion *et al*[51] studied 102 patients with IBD who underwent in a single examination, initially a WLE with random biopsies, then a targeted biopsy protocol and finally, DCE with targeted biopsies. They reported that biopsies obtained by the latter method detected significantly more dysplastic lesions than random biopsies with WLE ($P = 0.001$), as well as more than WLE with targeted biopsies ($P = 0.057$).

According to Subramanian *et al*[52] meta-analysis study including a large number of patients, the overall difference between the DCE and WLE in the detection of dysplasia was approximately 7% (95%CI: 3.2-11.3), with the former showing a better rate of dysplastic lesions detected by targeted biopsies, as well as a higher rate of detection for flat lesions at 27% (95%CI: 11.2-41.9). On the other hand, the omission of random biopsies during chromoendoscopy will result in missing endoscopically invisible dysplasia. According to another meta-analysis, Wu *et al*[47] reported that DCE offers median to good sensitivity and a very good accuracy for revealing lesions with dysplasia in UC after analyzing six randomized controlled trials with 1.528 patients. The pooled sensitivity and specificity for DCE with targeted biopsies were 83.3% (95%CI: 35.9%-99.6%) and 91.3% (95%CI: 43.8%-100%) respectively, with conventional colonoscopy demonstrating lower rates. Soetikno *et al*[53] in a well-designed meta-analysis with 665 patients with IBD, demonstrated that the pooled positive percentage of DCE over WLE for the

discernment of dysplasia of any grade per patient was 7% (95%CI: 3.3%-10.3%), as well as the possibility to miss dysplasia was 93% lower by performing chromoendoscopy with targeted biopsies (the pooled OR was 0.07; 95%CI: 0.03-0.21). Interestingly, according to a prospective study, Marion *et al*[54] showed that apart from the superiority of DCE when compared to WLE, a DCE examination without any findings was considered as the most probable indicator for a patient without any level of dysplasia, whereas an exam with any sort of findings was positively correlated with earlier referral for colectomy(hazard ratio, 12.1; 95%CI: 3.2-46.2).

Nevertheless, lately, the advantages of DCE over WLE have come into question, as well as the practicability of applying DCE in a real world setting of hectic endoscopy units. Trying to highlight this problem, a large retrospective non-randomized trial with different types of endoscopes used over time showed that the performance of DCE for IBD surveillance did not increase detection of dysplasia compared with WLE with targeted and random biopsies (11% *vs* 10%, P = 0.80)[55]. The number of lesions with neoplasia was also comparable between the DCE and WLE groups (P = 0.30).

As a final point, an interesting cohort analysis regarding cost-effectiveness was conducted by Konijeti *et al*[56], that compared DCE with targeted biopsies to WLE with random biopsies at various surveillance intervals and no surveillance at all. Chromoendoscopy was more efficient in the detection of dysplasia and cost more effective when compared with WLE. DCE exhibited cost-effectiveness relative to patients not undergoing any surveillance when performed at intervals bigger than 7 years.

VIRTUAL CHROMOENDOSCOPY SYSTEMS

Technological progression has enabled newer modalities based on older technologies for mucosal assessment. Given the success rate of chromoendoscopy in assessing colonic mucosa, the newest endoscopic devices have filters and algorithms that enable the mimicry of chromoendoscopy by filtering some light wavelengths to better underline abnormal tissues, while foregoing the limitating factors of chromoendoscopy. Dye-less or virtual chromoendoscopy has been developed by three major manufacturers for their respective endoscopic platforms. NBI filters out red and green light bands while contributing more to blue light bands at the 415 nm wavelength. This modality allows for visualization of the vasculature of the upper mucosa and different patterns correlating to different degrees of mucosal inflammation and predicts disease relapse. In the same vein, the i-Scan system provides detailed analysis, which is based on principles similar to NBI, with parameters allowing the processing of light through specific algorithms. This process provides detailed analysis based on vessel, mucosal pattern or surface architecture (i-Scan v, i-Scan p and i-Scan SE, respectively), with each analysis being readily available during endoscopy[57].

It has been reported that the yield of surveillance can be improved by the use of autofluorescence with NBI[36]. According to a study by Dekker *et al*[34], 52 suspicious lesions were detected in 17 patients using NBI, in comparison to 28 lesions in 13 patients detected with WLE. The pathology of the targeted biopsies revealed neoplasia in 11 patients; neoplasia was detected in 4 patients with both those modalities, in another 4 neoplasia was detected only by use of NBI, and in 3 patients neoplasia was discovered only by WLE, demonstrating non-statistical significance (P = 0.705) for those three modalities. In addition to targeted biopsies, 1522 random biopsies were taken in the context of surveillance. The pathology of these biopsies added only 1 patient with dysplasia that remained undetected by both NBI and WLE[34]. A prospective multicenter study by Leifeld *et al*[35] concluded that the two techniques did not differ in the statistical probability of lesion detection, but NBI required less withdrawal time (23 min *vs* 13 min, respectively P < 0.001) and biopsy samples (11.9 *vs* 38.6 biopsy specimens, respectively P < 0.001), when compared to WLE. These results are backed by a randomized study by Ignjatovic *et al*[38], which revealed no difference between the two modalities, regarding the detection of dysplasia. Overall, NBI does not seem to achieve a significantly higher probability of dysplasia detection, compared to conventional HD colonoscopy.

In the same vein Pellisé *et al*[58] conducted a prospective, randomized, controlled trial comparing NBI to DCE in 60 patients with long-standing inactive colonic IBD. The authors reported that NBI was less time-consuming (P < 0.01), equally effective in detecting dysplastic lesions and had a lower rate of false-positive biopsies (P = 0.001). However, NBI missed suspicious lesions with a non-significant miss rate difference of 30.7% (95%CI: -64.2% to 2.8%). As a result, the study surmised that NBI should not be standard modality for surveillance.

In general, NBI did not substantially differ from DCE, a claim that needs to be verified by more robust data pooling. A possible explanation is that NBI can more readily identify non-neoplastic inflammatory lesions than WLE, which were not pooled in the meta-analysis comparing those techniques[37]. Furthermore, the iterations of NBI are different in those studies, with older generation systems producing suboptimal, darker images[37,42]. Based on the current level of evidence, DCE remains the standard technique for the surveillance in IBD patients.

A large randomized prospective study comparing HD-iScan and HD-WLE to standard DCE did not prove inferiority for those two techniques, with the question of whether i-Scan and HD-WLE will benefit an expert endoscopist remaining unanswered[39]. The authors conclude that they need more multiple-operator studies

to assess the helpful potential of these new techniques.

CONFOCAL LASER ENDOMICROSCOPY

One of the newest tools in the arsenal of mucosal assessment for dysplasia is the confocal laser endomicroscopy (CLE) that allows *in vivo* microscopic inspection and evaluations of a targeted lesion in the gastrointestinal tract. This new and evolving method is used in conjunction with HD-WLE and DCE to further define suspicious lesions and assess their histology, by performing real time analysis of the cellular and subcellular characteristics at high resolution. The technique is based on fluorescence, which requires the addition of fluorescein intravenously or topically, but results in high quality images, comparable to traditional histology.

Kiesslich *et al*[59] first used the endoscope-based integrated system in 2007 to demonstrate that neoplastic changes in patients with UC can be identified with very good accuracy (94.7% sensitivity, 98.3% specificity, 97.8% accuracy), compared with standard surveillance endoscopy. Overall, 4.75-fold more neoplastic areas could be identified than with a WLE (P = 0.005), while requiring only half the number of biopsy samples (median 21.2 in the CLE group *vs* 42.2 undergoing surveillance endoscopy), despite the fact that CLE prolonged colonoscopy by an additional 10 min on average (P > 0.05). A recent study by Wanders *et al*[60], on the application of integrated CLE for surveillance in CD, which was terminated early due to critical equipment failure at 4 of the 5 participating centers, came up with a much lower diagnostic yield, with sensitivity of 42.9%, specificity of 92.4% and accuracy of 86.7%. The authors concluded that the technique probably will not be used in the daily practice of screening for CRC in patients with colitis.

A recent study of the probe-based CLE (pCLE) comes from Sweden where it was used for the surveillance of dysplasia in patients with PSC-IBD, a population with 6-fold increase in the incidence of CRC compared with the average risk for CRC population[61]. The study showed good diagnostic accuracy, with the estimated accuracy at 96%, sensitivity at 89% and specificity at 96%, with a low PPV at 41%, but with a very high NPV at 99% for the pCLE. The authors noted that the yield for accuracy fell when assessing areas with mucosal inflammation being misinterpreted as dysplasia. This study challenges the earliest attempts at pCLE systems for CRC surveillance in IBD patients by van den Broek *et al*[62], where the authors reported much lower diagnostic yield.

CONCLUSION

Despite the fact that DCE with targeted biopsies is the gold standard technique for IBD surveillance, it has some limitations. The need for adequate bowel preparation, the long procedure time, and its operator dependence are some of them. Moreover, the presence of active mucosal inflammation or post-inflammatory polyps may affect the images of chromoendoscopy and, in these cases random biopsies are still justified. There are no sufficient data about the effectiveness of the different dyes in detecting dysplasia and there are some concerns about methylene blue inducing DNA damage but have not yet been validated. Two recent editorials have questioned the SCENIC consensus, because chromoendoscopy and targeted biopsies have not been shown to improve CRC mortality[63,64]. Even when accounting for those limitations, chromoendoscopy remains a validated technique that becomes more and more recommended for CRC surveillance in IBD patients, whilst white light endoscopy with random biopsies should only be performed when the skill or the equipment for chromoendoscopy is unavailable.

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P- Reviewer: Gkekas I, Lorenzo-Zúñiga V, Muguruma N, Osawa S
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 259-266

DOI: 10.4253/wjge.v10.i10.259

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic retrograde cholangiopancreatography-induced and non-endoscopic retrograde cholangiopancreatography-induced acute pancreatitis: Two distinct clinical and immunological entities?

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Author contributions: Plavsic I and Hauser G designed and conduct research and are the guarantors of this work; Plavsic I, Hauser G, Žitinić I, Mikolasevic I, Poropat G contributed to the discussion and reviewed/edited the manuscript; Plavsic I, Poropat G and Hauser G analysed collected data; Plavsic I, Hauser G and Žitinić I wrote the paper.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Supported by an education grant from Unicersity of Rijeka, No. 963./2018.

Manuscript source: Invited manuscript

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Received: May 18, 2018
Peer-review started: May 18, 2018
First decision: June 4, 2018
Revised: June 10, 2018
Accepted: August 1, 2018
Article in press: August 1, 2018
Published online: October 16, 2018

Abstract

Acute pancreatitis (AP) is common gastrointestinal disease of varied aetiology. The most common cause of AP is gallstones, followed by alcohol abuse as an independent risk factor. With the increased need for invasive techniques to treat pancreatic and bile duct pathologies such as endoscopic retrograde cholangiopancreatography (ERCP), AP has emerged as the most frequent complication. While severe AP following ERCP is rare (0.5%), if it does develop it has a greater severity index compared to non-ERCP AP. Development of a mild form of AP after ERCP is not considered a clinically relevant condition. Differences in the clinical presentation and prognosis of the mild and severe forms have been found between non-ERCP AP and post-endoscopic pancreatitis (PEP). It has been proposed

that AP and PEP may also have different immunological responses to the initial injury. In this review, we summarise the literature on clinical and inflammatory processes in PEP *vs* non-ERCP AP.

Key words: Acute pancreatitis; Endoscopic retrograde cholangiopancreatography; Post endoscopic retrograde cholangiopancreatography pancreatitis

Core tip: Acute pancreatitis (AP) is the most frequent complication after endoscopic retrograde cholangiopancreatography (ERCP) and although low prevalence is found, if it develops it has greater severity index compared to non-ERCP AP. The differences in factors influencing appearance, clinical presentation and prognosis of ERCP induced and non ERCP induced AP were found, lead to opinion that mechanism by which they induce inflammation, may also be different. It would be of great importance to find immunological components that can distinguish patients with tendency to develop severe AP from patients with mild form, especially in ERCP induced AP where organ failure occurs half time earlier.

Plavsic I, Žitinić I, Mikolasevic I, Poropat G, Hauser G. Endoscopic retrograde cholangiopancreatography-induced and non-endoscopic retrograde cholangiopancreatography-induced acute pancreatitis: Two distinct clinical and immunological entities? *World J Gastrointest Endosc* 2018; 10(10): 259-266 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/259.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.259

INTRODUCTION

Acute pancreatitis (AP) is a common gastrointestinal disease with a reported incidence of 13-45 cases per 100000 persons annually[1]. According to the revised Atlanta classification, diagnosis of AP requires two of three following features: upper abdominal pain of acute onset, often radiating through to the back; serum amylase or lipase activity greater than three-times the normal level; and findings on cross-sectional abdominal imaging consistent with AP[2]. The severity of AP can be divided into mild, moderately severe or severe forms based on the presence or absence of persistent organ failure and local and systemic complications (Table 1). The mild form of AP is characterised by inflammation and the synthesis of proinflammatory cytokines in the affected area. The moderate and severe forms are characterised by the release of proinflammatory molecules into the circulation, causing systemic inflammatory response syndrome (SIRS)[3].

Gallstones are most common cause of AP, followed by alcohol abuse as an independent risk factor[2].

Invasive techniques used for the treatment of pancreatic and bile duct pathologies, such as endoscopic retrograde cholangiopancreatography (ERCP), carry a certain risk of complications. The most frequent of these is AP. Large variations in the reported incidence and severity of post-endoscopic pancreatitis (PEP) has led to unobjective risk evaluation, mostly consisting of retrospective studies. Kochar *et al*[4] reported an overall PEP incidence of 9.7%, while in high-risk patients the incidence was 14.7%. It is important to record why ERCP is performed, whether for therapeutic or diagnostic reasons, as patients may have an underlying condition that may affect the incidence of complications[5]. Most records report increased PEP after therapeutic ERCP[6].

AP is a disease of varied aetiology. Each produces a similar disease pattern, indicating that they all converge at a common point to initiate a cascade of events resulting in AP[7,8]. Messmann *et al*[5] found that people with AP are usually admitted to hospital several hours or even days after the initiation of symptoms. Therefore, it is impossible to determine the exact time of injury and initiation of the inflammatory phase. Instead, studies use PEP as a human model to examine the initial cytokine and acute-phase response in the first hours after initiation. It has been reported that PEP can serve as an ideal model for investigating the initial inflammatory phase in non-ERCP-induced AP.

An alternate opinion is that AP and PEP may actually be different disorders. This assumption is based on the differences in clinical presentation and prognosis of the mild and severe forms[9,10]. The triggers for the two disorders differ, and consequently, the mechanism by which they induce inflammation may also differ[11].

CLINICAL PRESENTATION

Different clinical outcomes of non-ERCP-induced AP and PEP have been found in several studies[9,10,12] (Table 2). Patients that developed post-ERCP pancreatitis initially had a higher APACHE Ⅱ score (key prognostic factor in predicting mortality) compared to AP of other aetiologies[10]. The APACHE Ⅱ score takes approximately 48 h to achieve a good predictive index. Therefore, whether this score represents a good method to differentiate initial disease severity prognosis (within 24 h), and if it can be reliably used to compare non-ERCP AP and PEP, remain questionable[9].

As mentioned earlier, severe AP following ERCP is rare (0.5%), but if it does develop, it does so with a greater severity index when compared to non-ERCP AP. Fung *et al*[10] reported that the extent of parenchymal necrosis is greater in PEP patients. There was also a higher rate of infected necrosis in the PEP group in their study. In PEP, the infection occurs earlier than in acute non-ERCP-induced pancreatitis. Due to small number of patients with ERCP induced acute necrotising pancreatitis (ANP) and low statistical power of their study, results should be interpreted with caution. All the same, these results should be taken into consideration, since the presence of infection and its extent is more important

Table 1 Severity of acute pancreatitis

Mild	Absence of both (peri) pancreatic necrosis and organ failure
Moderate	Presence of sterile (peri) pancreatic necrosis and transient organ failure
Severe	Infected (peri) pancreatic necrosis or persistent organ failure

for disease prognosis than pancreatic necrosis[10]. Organ failure develops early in the severe form of AP, either present at admission or 24 h later. In PEP, organ failure occurs twice as fast as in non-ERCP AP[3].

The mild form of ERCP-induced pancreatitis has a shorter and milder disease course with only a temporary increase in the level of enzymes in the blood (up to 48 h), suggesting a non-specific pancreatic reaction to injury, not necessary inflammation. Patients with mild post-ERCP pancreatitis have been reported to have a significantly shorter duration of pain and need for analgesia and parenteral hydration. All patients involved in this study, indicated for ERCP, were studied after they had been discharged from hospital because the acute condition can influence the intensity of inflammation[9]. Studies on drug effectiveness on the prevention of post-ERCP AP use the reduction in total post-ERCP AP incidence as the final measurement. So far, results have shown a reduction in the mild form but not the severe form. The primary goal should be a reduced incidence of severe PEP, as the mild form is not a clinically relevant condition[13-16].

MECHANISM OF INJURY

Non-ERCP pancreatitis

As previously mentioned, the most common causes of non-ERCP AP are gallstones and alcohol abuse[2]. The primary location of injury for both causes are acinar cells[17]. Gallstones lead to duct obstruction and blocking of acinar exocytosis, leading to the colocalization of zymogen and lysosomal granules and early activation of pancreatic enzymes. Alcohol leads to oxidative and non-oxidative damage. The non-oxidative pathway involves increased levels fatty acid ethyl ester, whereas the oxidative pathway is characterised by the accumulation of acetaldehyde, acetate and NADH. Alcohol also modifies the intracellular redox state by diminishing the NAD/NADH ratio and increasing the lactate/pyruvate ratio, ultimately leading to metabolic alterations and acinar cell injury[18].

Post-endoscopic pancreatitis

The factors influencing PEP incidence are multifactorial. These include patient-related factors, operator-related factors and method-related factors. Patient-related factors involve age, sex, pre-existing pancreatitis, prior history of post-ERCP pancreatitis, sphincter of Oddi dysfunction, and small bile duct and pancreatic divisum. Operator-related factors are associated with the experience of the endoscopist. The method-related factors are the most important because in them lies the greatest possibility for controlled intervention. Method-related factors cause mechanical injury a number of different ways. Combined operator and method- related factor as repeated and difficult papilla cannulation can lead to oedema and obstruction of free juice flow and sphincter of Oddi spasm. This mechanism may resemble the damage caused by gallstone obstruction. Furthermore, osmolarity and the ionic nature of the contrast media can cause chemical injury. Injecting contrast media are responsible for hydrostatic injury, which is one of the main causes of pancreatitis after ERCP[19]. Another factor is increased duct pressure, which can cause early activation of pancreatic enzymes[20]. However, microbiological factors related to contaminated endoscope and translocation from the intestines is not considered to play a major role.

INFLAMMATORY PROCESS

General

It is considered that the first pancreatic event, in any of these circumstances, occurs at the level of acinar cells[21]. Intrapancreatic trypsinogen activation and NFκB activation represent the two main initial triggers for AP[8,22]. Sah *et al*[22] reviewed studies that used animal models to show that NFκB activates and induces inflammation without the need for trypsinogen activation. Therefore, these two events represent two independent cellular events.

The early events in AP include inhibition of zymogen secretion, altered intracellular Ca^{2+} homeostasis that modifies pH values (Figure 1), intrapancreatic activation of trypsinogen and other zymogens and activation of cell death pathways (NFκB)[8,18].

The initial injury of the acinar cells caused by zymogens is sterile[23] (Figure 2).

Sterile inflammation requires two distinct signals through the activation of pattern recognition receptors (PRRs) (Figure 3). PRRs, like Toll like receptor (TLR) and NOD like receptor (NLR), are part of the innate immune response[23].

Randomised controlled trials have been used to study the use of allopurinol in the prevention of post-ERCP AP. Allopurinol reduces the production of uric acid. Uric acid uses DAMPs (NLR receptors) to trigger an inflammatory response. These studies found that allopurinol decreases the incidence of post-ERCP AP[24,25], indicating that the innate immune cells play a role in AP after ERCP[21]. Shamoon *et al*[26] in their study, emphasise the importance of innate immune cells and derived inflammatory mediators as therapeutic targets in AP in early phase of the disease (24-48 h).

The balance between pro- and anti-inflammatory immune response determines the prognosis in AP. A fall in the co-expression of HLA-DR on $CD14^+$ monocytes is considered a standard laboratory indicator of compensatory anti-inflammatory immune response syndrome (CARS)[27]. The severe form of AP is frequently associated with immune suppression, which increases the risk

Table 2 Differences in post-endoscopic pancreatitis *vs* non- endoscopic retrograde cholangiopancreatography induced acute pancreatitis clinical presentation

	PEP	non-ERCP-induced AP	Conclusion
Fung *et al*[10] ERCP-induced acute necrotising pancreatitis *vs* ANP induced by other causes	Higher APACHE Ⅱ scores on admission More extensive pancreatic necrosis Higher rate of infected necrosis	Lower APACHE Ⅱ scores on admission Less extensive pancreatic necrosis Lower rate of infected necrosis	ANP is more severe when ERCP-induced
Testoni *et al*[12] ERCP induced AP *vs* non ERCP induced AP		No statistical difference: severity of the pancreatitis mortality rate (double in severe PEP) hospitalisation	
	In mild form serum amylase fell 50% in 38.9 h. Peak serum amylase halved within 48 h in 92%	In mild form serum amylase fell 50% in 46, 4 h. Peak serum amylase halved within 48 h in 73.6%	Statistical difference ($P < 0.001$) Mild form of PEP a sort of pancreatic reaction, instead of true episode of acute pancreatitis
Abid *et al*[9] Mild form: ERCP induced AP *vs* non ERCP induced AP	Shorter duration of pain; Shorter time of intravenous hydration; Shorter time to resumption of oral diet; Shorter hospital stay ($P < 0.001$)		ERCP-induced AP mild attacks run a significantly shorter and milder course than non-ERCP related mild attacks

PEP: Post-endoscopic pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; AP: Acute pancreatitis.

Figure 1 Altered Ca^{2+} homeostasis- change from physiologic intracellular transient Ca^{2+} spikes to pathologically sustained global Ca^{2+} rise, can lead to significantly lower pH values and cause early enzyme activation.

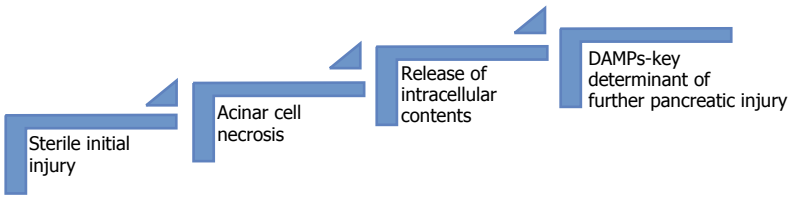

Figure 2 Sterile injury causes acinar cell necrosis, the release of intracellular contents, and activation of damage-associated molecular patterns that further determine pancreatic injury.

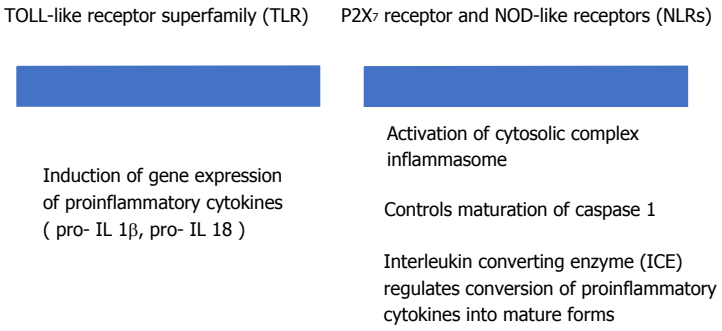

Figure 3 Activation of pattern recognition receptors.

of infection, organ failure and death[28]. Kylanpaa *et al*[3] reported that impaired cellular immunity causes complications related to infection in AP at a later stage of the disease. Furthermore, Testoni *et al*[12] reported that infection in PEP occurs during or immediately after the procedure. For this reason, infection in non-ERCP AP is considered a secondary event, while in PEP it is considered the primary event.

IMMUNE COMPONENTS

While the role of different cytokines in AP has been

extensively studied, the role of cellular immunity is poorly evaluated[28]. Innate immune cells are the major leukocyte population in the inflamed pancreas[29].

Monocytes and macrophages

Monocytes and macrophages are the main inflammatory cell populations in AP, and both play active roles in AP progression. The production of proinflammatory factors like tumour necrosis factor (TNF)-α in pancreatic cell stimulates the activation of macrophages in distal organs including the peritoneum, spleen, liver and lungs. Monocyte chemoattractant protein (MCP)-1 and macrophage migration inhibitory factor (MIF) play important roles in AP. Bhatia *et al*[30] reported that blocking MCP-1 synthesis reduces the severity of AP. Furthermore, antibodies against MIF improve survival in rats with AP[31]. The expression of HLA-DR on monocytes gives a good indication of monocyte function. In cases of immunosuppression, decreased monocyte HLA-DR expression predicts the development of organ failure[32].

Neutrophils

Neutrophils play a central role in the development of local and systemic complications, therefore, researchers have investigated the depletion of neutrophils as a therapeutic option for AP. Anti-neutrophil serum (ANS) exhibited a marked attenuation in intrapancreatic trypsin activation, ameliorated choline-deficient ethionine supplemented (CDE) diet-induced pancreatitis and completely prevented lung injury[33,34]. The depletion of neutrophils associated with ANS did not influence macrophage infiltration, but it did decrease the number of lymphocytes in the pancreas[29].

T cells

Progression of AP is accompanied by a change in the number and ratio of $CD4^+$ and $CD8^+$ lymphocytes[35]. $CD4^+$ lymphocytes are especially important as they act as co-stimulators of macrophage activation via antigen presentation and the release of proinflammatory cytokines. They have been reported to have a direct cytotoxic effect on acinar cells through Fas ligand expression[36]. Depletion of $CD4^+$ lymphocytes reduces the severity of AP[21]; however, $CD4^+$ lymphocytes are a heterogeneous population and some release IL-22, which has an anti-inflammatory effect[37].

Natural killer cells

Natural killer (NK) cells are predominantly studied in response to infection and immunosurveillance against tumours. They are part of the innate immune system, giving them the ability to respond without prior sensitisation. They also carry certain abilities of adaptive immunity, as they are primed during development, their receptors can exhibit antigen specificity, they undergo clonal expansion during infection and generate long-lived memory cells[38]. Natural killer cells can undergo clonal-like expansion through specific and non-specific immune responses. While the specific response occurs *via* interaction of their activating receptors with viral antigens, the non-specific response is driven by the production of cytokines and proliferation following exposure to proinflammatory cytokines in the absence of TCR signals and co-stimulation[39,40]. Natural killer cells have immunological memory, which enables them to react faster and more aggressively in familiar surroundings. The most important cytokines produced by NK cells after activation are TNF-α and IFN-γ[41]. It is thought that NK cells that produce proinflammatory cytokines can contribute to dysregulation of the immune response as seen in sepsis[42]. The cytokine IL-15 pays a role in the maintenance of NK cells. The half-life of mature NK cells is about 1 wk, but in the absence of IL-15 they disappear in 48 h. These cells can also serve as an immunotherapeutic target.

Dabrowski *et al*[28] reported significant depletion of the NK cell population on the first day of severe AP, while there was no significant change in NK cell number in mild AP. These findings are consistent with the idea that severe forms of AP are related to immune suppression. Profound inhibition of innate cell immunity can be explained by the migration of NK cells and natural killer T (NKT) cells to the site of inflammation.

Natural killer T cells

Natural killer T cells are generally autoreactive and can recognise both exogenous and endogenous ligands. There are two types of NKT cells, type Ⅰ and type Ⅱ. Type Ⅰ is more prevalent in mice and can be either pathogenic or protective, although they have a greater propensity to be pathogenic. Type Ⅱ is prevalent in humans, and predominantly protect against inflammation and autoimmune disease. Different self-antigens can stimulate type Ⅰ NKT cells, and some of these antigens are present at elevated levels during inflammation[43].

In patients with severe AP there is a reduction in the number of peripheral lymphocytes, especially monocytes and cytotoxic T lymphocytes[28,44].

Cytokines

The most important anti-inflammatory cytokine is interleukin (IL)-10. It down-regulates the production of proinflammatory cytokines and the expression of HLA-DR on monocytes. If the compensatory anti-inflammatory response is too intense, however, it may lead to immunosuppression and complications including infection. The concentration of IL-10 is highest in the early phase of severe AP. As infection is considered to be one of the prognostic factors related to disease severity, IL-10 may be a promising predictive marker of organ failure[45]. There are conflicting reports for the use of IL-10 in the prevention of post-ERCP AP. In a randomised double-blind study, Deviere *et al*[46] showed a reduced incidence of post-ERCP AP after IL-10 usage, although this was not supported by a study by Dumot *et al*[47].

As a key proinflammatory mediator, IL-6 regulates

the synthesis of acute-phase proteins in the liver as well as macrophage-conditioned tissue damage[48]. It reaches its peak value 24-48 h after clinical expression. In necrotising pancreatitis, the peak levels of IL-6 occur after 24 h[5]. Minkov *et al*[48] concluded that IL-6 represents an independent factor for predicting severity in acute non-ERCP pancreatitis.

The highest values of C-reactive protein (CRP) are recorded after 48–72 h, which is later than that of IL-6[5]. Although CRP has been identified as a late marker in laboratory monitoring[49], Messman *et al*[5] found that both IL-6 and CRP peak earlier in patients with ANP.

IL-1β-mediated signalling is required for full pancreatic and distal organ injury and inflammation[50], and is the pivotal inflammatory mediator in cell death associated with sterile inflammation[51]. Serum levels of IL-1β do not correlate with AP severity in humans, although it has been found that the values peak after 24 h and are greater in patients with severe AP compared to mild AP[52]. In animal models, peak serum IL-1β precede peak serum IL-6 values[50,53]. It is possible that IL-1β is required for the induction of IL-6 production, which is strongly correlated with disease severity in humans[54]. IL-1β and TNF-α are considered the primary cytokines that initiate and propagate most of the consequences of the SIRS in AP[55,56]. IL-6 prevents the synthesis of IL-1β and TNF-α[57].

Kilciner *et al*[49] compared early changes (within 24 h) in the serum levels of IL-2, IL-4, TNF-α and IL-6 in the development of post-ERCP pancreatitis. They used patients who underwent ERCP as well as a control group consisting of patients with non-ERCP AP caused by gallstones, drugs or alcohol. They found that IL-4, an anti-inflammatory cytokine, was significantly lower in post-ERCP and non-ERCP AP patients compared to patients who did not develop pancreatitis. The TNF-α level was not significantly different after 24 h in patients who developed PEP compared to those who did not develop pancreatitis after ERCP. After 24 h, the IL-6 levels did not differ from the control group, but they were significantly higher compared to patients who did not go on to develop pancreatitis after ERCP.

The role of IL-18 may depend on the presence of other cytokines. It plays an important role in the local immune response to pancreatic injury[23], and can also be found in serum. It has been described to prime NK cells, and NK cells that were unable to receive IL-18 signals were found to have defective cytotoxicity and cytokine secretion after stimulation[38].

AP is the most frequent complication after the ERCP procedure. Although the incidence of AP after ERCP is low, it is reported to occur in 0.5% of patients, PEP has a greater severity index compared to non-ERCP AP[10]. As the mild form of PEP is not a clinically relevant condition, it would be useful to identify early markers to predict whether a patient will develop the severe form of PEP.

The serial changes in amylase and lipase levels in patients without PEP suggest the existence of subclinical pancreatic damage. Messmann found that amylase and lipase levels increased equally among all patients after ERCP[5]. Amylase and lipase are released into the systemic circulation due to disturbed transport and increased ductal permeability; however, they are not thought to be responsible for inducing further inflammation. Based to these findings, we conclude that serum amylase values can't serve as an adequate future therapeutic goal.

The role of cytokines, especially IL-10, IL-6 and TNF-α, have been extensively studied for the prediction of disease severity[45,48,55,56]. These cytokines can be used to predict the severity of PEP after 12-24 h; however, measurements taken 4 h after the procedure showed no significant difference between patients who developed PEP and those who did not develop PEP[51,58].

Further research on the initial inflammatory response is necessary, particularly as organ failure has been reported to occur earlier in severe forms of AP, either at admission or 14 h later. Furthermore, in PEP, organ failure occurs twice as fast than in non-ERCP AP[44]. Direct comparison of the initial inflammatory response between PEP and non-ERCP AP would be of significant importance to clarify these statements. Found difference in clinical response to initial injury might be explained by different initial immune response[59].

Infection is considered to be the most important prognostic factor for disease severity. Similarities between cytokines and inflammatory mediators in sepsis and AP are often compared. Kjaergaard *et al*[60] reported that the expression of NKG2D receptors on NK cells and CD14 on monocytes can be valuable prognostic markers of an unbalanced immune response, and may predict a worse outcome for critically ill patients. Also, Guo *et al*[61] presented natural killer cells as critical to eliminate pathogens during the early phase of sepsis and prevent patients from developing secondary infection. We suggest that similar components should be used in PEP and non ERCP AP.

In addition to searching for adequate biomarkers to assess disease severity, it is our opinion that novel therapeutic strategies for both of these conditions lie in uncovering the immune pathways.

CONCLUSION

The most frequent complication after ERCP is AP. In most cases, it is not a clinically relevant condition, but in 0.5% of patients it has a greater severity index compared to non-ERCP AP. In severe PEP, infection occurs earlier than in acute non-ERCP-induced pancreatitis, and organ failure occurs twice as fast. Treatment of AP, regardless of the cause, is primarily supportive and implies a certain economic burden in the healthcare system worldwide. More thorough clarification of disease pathogenesis is needed, in order to find adequate immune target to predict and consequently prevent severe form of the disease.

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P- Reviewer: Gkekas I, Mohamed AA, Tahiri MJH, Venu RP
S- Editor: Cui LJ **L- Editor**: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 267-273

DOI: 10.4253/wjge.v10.i10.267

ISSN 1948-5190 (online)

MINIREVIEWS

Concise review on the comparative efficacy of endoscopic ultrasound-guided fine-needle aspiration *vs* core biopsy in pancreatic masses, upper and lower gastrointestinal submucosal tumors

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Author contribution: Khoury T and Mizrahi M contributed to the conception and design; all authors contributed to the analysis and interpretation of data; Khoury T and Mizrahi M contributed to drafting the manuscript; all authors approved the final version to be published.

Conflict-of-interest statement: The authors report no conflict of interest regarding this manuscript.

Manuscript source: Invited Manuscript

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Received: May 10, 2018
Peer-review started: May 10, 2018
First decision: June 8, 2018
Revised: July 2, 2018
Accepted: July 23, 2018
Article in press: July 23, 2018
Published online: October 16, 2018

Abstract

Endoscopic ultrasound (EUS)-guided fine needle aspiration with or without biopsy (FNA/FNB) are the primary diagnostic tools for gastrointestinal submucosal tumors. EUS-guided fine needle aspiration (EUS-FNA) is considered a first line diagnostic method for the characterization of pancreatic and upper gastrointestinal lesions, since it allows for the direct visualization of the collection of specimens for cytopathologic analysis. EUS-FNA is most effective and accurate when immediate cytologic assessment is permitted by the presence of a cytopathologist on site. Unfortunately, the accuracy and thus the diagnostic yield of collected specimens suffer without this immediate analysis. Recently, a EUS-FNB needle capable of obtaining core samples (fine needle biopsy, FNB) has been developed and has shown promising results. This new tool adds a new dimension to the diagnostic and therapeutic utility of this technique. The aim of the present review is to compare the efficacy of EUS-FNA to that afforded by EUS-FNB in the characterization of pancreatic masses and of upper and lower gastrointestinal submucosal tumors.

Key words: Efficacy; Safety; Gastrointestinal masses;

Fine needle aspiration and biopsy

Core tip: Endoscopic ultrasound (EUS)-guided sampling is the first diagnostic option for gastrointestinal submucosal and pancreatic lesions. In the past, fine needle aspiration (FNA) was the main method to obtain tissue for histological examination, however, it was associated with limited diagnostic accuracy. In the last decade, fine needle biopsy (FNB) needle was introduced into clinical practice, which allows for more tissue acquisition and improvement in diagnostic yield. In this updated minireview, we provide an overview on the role of EUS-FNA and FNB in certain gastrointestinal lesions. In addition, we provide a summary on the efficacy and safety profile of each procedure with reporting the recent guidelines recommendation.

Khoury T, Sbeit W, Ludvik N, Nadella D, Wiles A, Marshall C, Kumar M, Shapira G, Schumann A, Mizrahi M. Concise review on the comparative efficacy of endoscopic ultrasound-guided fine-needle aspiration *vs* core biopsy in pancreatic masses, upper and lower gastrointestinal submucosal tumors. *World J Gastrointest Endosc* 2018; 10(10): 267-273 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/267.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.267

INTRODUCTION

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered the initial diagnostic tool for the assessment of gastrointestinal lesions including pancreatic, submucosal, and lymphatic lesions[1]. Despite the extensive utilization of this technique, it possesses several key limitations. Among these limitations is the wide variability in the diagnostic yield of collected specimens, as well as the loss of histological architecture in the obtained specimens.

The variability of yield is currently mitigated by performing cytopathologic examination on site immediately after the collection of the specimen. Furthermore, onsite cytopathologic evaluation not only increases diagnostic yield, but does so more efficiently, permitting fewer needle passes and, presumably, decreasing the risk of complications[2,3]. Unfortunately, onsite cytopathologic evaluation is not widely available. Therefore, the ability to offer quality EUS-FNA is geographically restricted to those centers with cytopathology.

In addition, FNA is unable to adequately preserve tissue architecture for histopathologic analysis. This is particularly important in the evaluation of gastrointestinal stromal tumors and lymphomas[4,5]. Furthermore, FNA is unable to provide adequate tissue for further analysis with immunohistochemistry, phenotyping, or genetic analysis so as to allow for personalized treatment.

Fortunately, a novel EUS-fine needle biopsy (FNB) has been developed, permitting the collection of core biopsies *via* an endoscopic approach. This technique has been examined in several studies and has been found to enable the acquisition of large amounts of tissue with conserved architecture sufficient for histologic analysis[6,7]. In recent years, several studies reported the diagnostic yield of EUS-FNA and EUS core needle biopsy for various gastrointestinal lesions. Thus, the aim of the present minireview is to compare the efficacy of EUS-FNA *vs* EUS-FNB of various gastrointestinal lesions.

EUS-GUIDED FNA AND FNB

Currently, two subsets of needles are available for tissue acquisition (FNA and FNB). In the beginning, only FNA needles were available and the size of the needle was either 19 or ranged from 22 to 25-gauge. Once FNB needles were developed, they initially utilized the Trucut biopsy needle (QuickCore® needle; Cook Medical Inc., Winston-Salem, NC, United States), but its production was stopped later due to its overloaded firing mechanism and adverse events. Since then, three different FNB needles have been produced, which are easier to use than FNA needles. Examples include the Procore® needle, which is characterized by a cutting bevel (reverse for 19, 22 and 25-gauge and 20-gauge antegrade beveled side slot) at the needle tip (Cook Medical Inc.), the Acquire™ end-cutting needle, which is characterized by a three-point needle tip (22 and 25-gauge; Boston Scientific Corp., Marlborough, MA, United States), and the SharkCore™ needle, which is characterized by six distal cutting edges at the needle tip (19, 22 and 25-gauge; Medtronic, Minneapolis, MN, United States)[8]. Regarding needle sizes, several studies have examined the impact of needle sizes on diagnostic accuracy and yield. Generally, a larger needle size (19 gauge) will obtain more tissue for histological assessment than the smaller 22 and 25-gauge needles. However, the limiting factor in usage of 19-gauge needles is its higher rate of complication and technical failure. On the other hand, the smaller needle sizes (22 and 25-gauge) are more technically feasible[8]. Moreover, when cytology is supposed to be enough for making a diagnosis, such as the case in pancreatic lesions, previous meta-analysis demonstrated similar diagnostic yield of 22 and 25-gauge needles and non-superiority of the larger 19-gauge needle in diagnostic yield[9]. On the other hand, when tissue histology and architecture are needed for better assessment, such as in the case of gastrointestinal stromal tumors (GIST), lymphoma and autoimmune pancreatitis, a larger 19-gauge needle is preferred. A retrospective study reported the diagnostic yield of the SharkCore™ needles with EUS-FNA needles of solid upper gastrointestinal masses. More histological specimens were obtained with the SharkCore™ needles compared to EUS-FNA needles (59% *vs* 5%, $P < 0.001$)[10]. Furthermore, a recent study compared the SharkCore™ biopsy needle with

a standard EUS-FNA needle in cases of suspected gastrointestinal stromal tumors. Tissue adequacy was obtained in 100% in EUS-FNB as compared to 65% in the EUS-FNA groups (P = 0.006). A diagnosis was reached by immunohistochemical staining in 52.7% of cases compared to 87% in the EUS-FNA group (P = 0.01)[11].

SAFETY PROFILE

EUS-FNA has been associated with a high safety profile with minor intra- and post-procedural adverse events[12]. Moreover, the ASGE standards of practice committee has reported EUS-FNA to be a procedure with a high safety profile[13]. A recent systemic review article of 51 studies with 10941 patients overall reported EUS-FNA-related morbidity and mortality of 0.98% and 0.02%, respectively, with an acute pancreatitis rate of 0.44% and post-procedure pain occurring in 0.34% of patients[14]. Another systemic review that focused on EUS-FNA of pancreatic cystic lesions (40 studies, 5124 patients) reported overall morbidity of 2.66% and mortality of 0.19%[15].

EUS-guided core biopsy using the 19-gauge Trucut needle [notably, Trucut Biopsy needle (EUS guided) is no longer being used, as the company stopped making this needle] has also been reported to be safe, with an adverse events rate reaching up to 2%[16]. This is reflected throughout the literature by an accumulation of evidence on the safety of these procedures, indicating a relatively similar complication rate between them of 1%-2%[17]. Moreover, another study has reported minor conservatively treated complications of low-grade fever and asymptomatic pneumoperitoneum in the immediate post-procedural time, with none of the patients experiencing major or life-threatening complications[18]. The newer above-mentioned FNB needles were shown to have a high safety profile without increased risk or procedure-related complications. Finally, several studies demonstrated that there was no difference in morbidity and mortality between EUS-FNA and FNB procedures[11,19,20].

EUS-FNA *VS* FNB IN PANCREATIC MASSES

Rapid and accurate diagnosis of pancreatic masses is very important given the poor prognosis associated with pancreatic cancer. EUS-FNA is the main initial diagnostic modality for tissue acquisition of pancreatic lesions[21,22]. Recently, the European society of gastrointestinal endoscopy (ESGE) released recommendation for the diagnosis of pancreatic lesions. ESGE recommends EUS-guided sampling for pathological diagnosis as a first diagnostic test (Strong recommendation, moderate quality evidence). In the case of the presence of suspected pancreatic malignancy with negative or indeterminate diagnosis, ESGE recommends either performing revision on the initial pathology specimens obtained or to repeat EUS-guided tissue acquisition or surgery (Weak recommendation, low quality evidence). For pancreatic cystic lesions, ESGE recommends EUS-guided tissue acquisition for biochemical and cytological evaluation, except for radiologically appearing benign cysts less than 1 cm in diameter (Strong recommendation, low quality evidence)[23].

The reported diagnostic accuracy of EUS-FNA for pancreatic mass lesions is variable and ranges from 78% to 95%[24], the sensitivity and specificity were reported to be 64% to 95% and 75% to 100%, respectively[24,25]. This value is declining for EUS-FNA in other organs such as mediastinal masses and gastrointestinal stromal tumors[26,27].

The diagnostic yield of EUS-FNA might be adversely affected in the absence of onsite cytopathologic assessment[28,29]. Furthermore, in the setting of chronic pancreatitis, the accuracy is declining[30]. A previous study by Gleeson *et al*[31] reported a 5%-7% false positive rate when obtaining tissue for cytological examination by EUS-FNA. To overcome this disadvantage, a new fine needle biopsy was used in pancreatic lesions, and subsequently there was an increased trend for the application of an FNB device designed to have a reverse bevel at the tip to obtain a core sample. It contains the characteristics of both FNA and a core biopsy needle[32]. This needle features greater flexibility for improved core tissue collection. In comparing the efficacy between FNA and FNB, a previous study demonstrated similarity in the diagnostic yields of EUS-FNB and EUS-FNA[33]. In these studies, both needles were similar in diagnostic accuracy for malignant lesions, however the number of needle passes to obtain adequate tissue was significantly lower in the FNB group. Another study by Atalawi *et al*[34] demonstrated that the sensitivity for pancreatic cancer diagnosis was 98%, while the specificity reached 100%. Moreover, another study showed that FNB was associated with significantly higher diagnostic yield compared to FNA (93.8% *vs* 28.1%, $P < 0.01$)[35]. Several other studies have shown superiority of EUS-FNB over the FNA method in obtaining adequate histopathological samples and higher diagnostic yields[32,32-38]. Additionally, Aadam *et al*[36] reported a significant rescue effect of FNA crossover to FNB. A recently released ESGE guideline recommended the use of 25 or 22-gauge needles for sampling pancreatic solid masses with no difference between FNA of FNB needles[39]. However, in the case of requirement for complete tissue architecture, such as lymphoma and GIST, the ESGE guideline recommends the use of a large bore FNB needle (19 or 22-gauge)[39].

EUS-FNA *VS* FNB FOR UPPER GASTROINTESTINAL SUBMUCOSAL TUMORS

Submucosal tumors of the gastrointestinal system are most frequently located in the stomach and the

proximal small intestine[40]. Nevertheless, they may present in any part of the gastrointestinal tract. The most common subepithelial tumors are GISTs[41-44]. In the past, the most widely accepted approach was surgical extraction of these gastrointestinal masses. However, there is increasing evidence supporting the need for precise histological diagnosis that could alter the patient's management and prevent unnecessary surgeries for asymptomatic and benign lesions[45-49]. The use of cytological examination has been questioned by several previous reports. For example, FNA of gastrointestinal submucosal tumors was associated with only 61% diagnostic accuracy[50]. Wittmann *et al*[51] reported no difference between FNA and the Procore needle. Bang *et al*[52] found a similar diagnostic accuracy and number of needle passes needed for pathological diagnosis by using 22-gauge FNA and FNB techniques. However, this study was limited by a very small number of participants. During the last several years, different needles were implemented into clinical practice to improve the diagnostic yield of gastrointestinal submucosal lesions. A previous study reported the pooled analysis of EUS-FNB for malignancy. The diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value reached 85.96%, 90.2%, 99%, 100% and 78.9%, respectively[53]. Another study showed that FNB was superior in extra-intestinal lesions[54].

Jeong *et al*[45] reported that the use of Trucut biopsy of submucosal tumors changed patient management in 30% of cases. Moreover, there is growing evidence supporting the use of EUS-FNB over FNA techniques[55] given its higher diagnostic yield. A recent randomized multicenter clinical trial using EUS-FNB showed feasible histopathological diagnosis of intestinal lesions with diagnostic accuracy of approximately 93% compared to EUS-FNA[53]. Another randomized controlled study reported a statistically significant better diagnostic yield of EUS-FNB compared to EUS-FNA in various gastrointestinal lesions[36] and, very recently, the use of FNB compared to FNA in gastric sub-epithelial tumors was associated with statistically significant higher diagnostic yield, higher proportion of adequate cellularity and reduced number of needle passes[56].

Although the literature is still lacking and only a few studies have been conducted, the present evidence might be sufficient to favor the use of FNB needles in gastrointestinal submucosal lesions until the establishment of guideline consensus in the field.

EUS-FNA *VS* FNB FOR RECTAL AND PERI-RECTAL TUMORS

Although EUS-guided procedures have been most studied for pancreatic and upper gastrointestinal lesions, they have also been used in the lower gastrointestinal tract. In this context, they are primarily useful for evaluation of rectal or perirectal lesions because of the difficult scope access beyond the rectum. Throughout the literature, there are only a few reports on FNA/FNB guided biopsy for lesions of the lower digestive tract[57-59]. Previous studies have reported equal efficacy of FNA and FNB and similar diagnostic accuracy in 10 of 11 patients[59]. Similarly, the diagnostic yield of EUS-FNA in rectal and sigmoid lesions (cancer and GIST) reached 90% in ten patients[57]. This diagnostic yield of EUS-FNA was consistent among other studies. Sasaki *et al*[58] reported a EUS-FNA diagnostic yield of 95.5% (21 of 22) in colorectal submucosal and extrinsic lesions. Prior studies have reported approximately 80%-90% diagnostic accuracy of EUS-FNA in diagnosing sub-epithelial tumors of the gastrointestinal tract[60,61]. On the other hand, a recent study has reported a decreased diagnostic accuracy of FNA/FNB in lower gastrointestinal lesions of approximately 50%[18]. Notably, this low accuracy was associated with small lesions less than 20 mm in size, suggesting that EUS-FNA/FNB may require further improvement for optimal diagnostic utility in the detection of smaller lesions. Furthermore, in this study, the use of FNB was effective as it was sufficient for tissue acquisition to make a diagnosis of recurrent lymphoma after failure of EUS-FNA to obtain sufficient material for histopathological examination. In seven patients, the specimen obtained by EUS-FNB led to changes in the presumptive diagnosis - two of them were later diagnosed with malignancy *via* FNB after having received a diagnosis of benign mass by FNA, while the remaining five patients were diagnosed as having malignancy according to FNA that later were ruled out *via* FNB[18]. Thus, EUS-FNB can be considered a complementary procedure to overcome the limitations of EUS-FNA to enhance histopathological diagnoses. Notably, some exaggerated interventions for benign lesions can be obviated given the higher diagnostic yield of EUS-FNB. Thus, although the reported literature is insufficient, there may be an argument for considering EUS-FNB as an initial diagnostic *vs* using it concurrently with FNA. Further studies are needed to establish the clinical applications and diagnostic accuracy of EUS-FNB needles in lower gastrointestinal tumors.

CONCLUSION

FNA and FNB are both accepted as safe procedures with a low complication rate of approximately 1%-2%. At present, FNA is best performed with immediate onsite cytopathologic review, which is not broadly available. FNB is not limited in this regard, and it further provides information on a tissue's architecture and provides a greater sample yield allowing for further analyses, such as genetic sequencing and phenotyping to be performed, thereby allowing for provision of a more personalized treatment plan. Recently, several guidelines have been published. Ang *et al*[8] addressed the enhanced diagnostic importance in tissue acquisition and improved diagnostic accuracy when using FNB needles. Moreover, recent ESGE released guidelines recommended the use of either FNA or FNB needles (22 or 25-gauge) for routine

Table 1 Summary of efficacy and safety of endoscopic ultrasound-guided fine needle aspiration with or without biopsy procedures

Procedure	Diagnostic accuracy	Safety (complications)	Mortality
Pancreatic, upper and lower GIST: Gastrointestinal stromal tumors; Submucosal tumors[1]			
EUS-FNA	Variable	Low	None
ROS available	High		
ROS unavailable	Low-moderate		
EUS-FNB	High	Low	
Other gastrointestinal lesions (lymphoma, GIST and chronic pancreatitis)			
EUS-FNA	Low	Low	None
EUS-FNB	High	Low	

[1]Excluding lymphoma, GIST and chronic pancreatitis. ROSE: Rapid on-site evaluation; GIST: Gastrointestinal stromal tumors; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; FNB: Fine needle biopsy.

EUS-guided sampling of solid masses and lymph nodes. However, when the aim of the sampling is to obtain core tissue with more preserved architecture, the ESGE recommended the use of smaller 19 or 22-gauge FNB needles (low quality evidence, weak recommendation)[39]. Thus, in light of current evidence, we recommend considering application of those recommendations, as it appears that a strong argument can be made for FNB given that it provides a greater amount of information with fewer needle passes and fewer resources without appreciably increasing the risk of complication to the patient (Table 1). Finally, the decision of the type and needle size should be individualized according to the suspected lesion to be sampled.

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P- Reviewer: Kwon YH, Sandhu DS, Skok P, Wang W
S- Editor: Cui LJ **L- Editor**: Filipodia **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2018 October 16; 10(10): 274-282

DOI: 10.4253/wjge.v10.i10.274

ISSN 1948-5190 (online)

MINIREVIEWS

Role of endoscopy in caustic injury of the esophagus

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Author contributions: Methasate A reviewed the literature and wrote the manuscript; Lohsiriwat V outlined the content and critically reviewed the manuscript.

Conflict-of-interest statement: The authors declared that we had no conflict of interest.

Manuscript source: Invited manuscript

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Received: April 30, 2018
Peer-review started: April 30, 2018
First decision: May 15, 2018
Revised: June 6, 2018
Accepted: June 28, 2018
Article in press: June 29, 2018
Published online: October 16, 2018

Abstract

Caustic injury of the esophagus is a problematic condition challenging endoscopists worldwide. Although the caustic agents and motives are different among countries and age groups, endoscopy still plays an invaluable role in diagnosis and treatment. Endoscopy can determine the severity of caustic ingestion which is of great importance in choosing appropriate treatment. However, some aspects of endoscopy in diagnosis of caustic injury remain controversial. Whether or not all patients need endoscopy, when to perform endoscopy and how to assess the severity are just some examples of these controversies. Due to lack of randomized controlled trials, many findings and suggestions are inconclusive. Computerized tomography scan of the chest and abdomen gains popularity in assessing the severity of caustic injury and avoiding unnecessary surgery. If esophageal stricture eventually develops, endoscopic dilatation is a mainstay. Maneuvers such as steroid injection and esophageal stent may be used in a refractory stricture. Nevertheless, some patients have to undergo surgery in spite of vigorous attempts with esophageal dilatation. To date, caustic injury remains a difficult situation. This article reviews all aspects of caustic injury of the esophagus focusing on endoscopic role. Pre-endoscopic management, endoscopy and its technique in acute and late phase of caustic injury including the endoscopic management of refractory stricture, and the treatment outcomes following each endoscopic intervention are thoroughly discussed. Finally, the role of endoscopy in the long term follow-up of patients with esophageal caustic injury is addressed.

Key words: Endoscopy; Diagnosis; Corrosive ingestion; Caustic injury; Esophagus; Stricture

Core tip: This mini-review comprehensively covered evidence-based endoscopy for caustic injury of the esophagus including pre-endoscopic management, endoscopic role in the acute and late phase of caustic injury, endoscopic management of refractory stricture and its outcomes. Tips and tricks to perform diagnostic and therapeutic endoscopy in these patients are also

discussed.

Methasate A, Lohsiriwat V. Role of endoscopy in caustic injury of the esophagus. *World J Gastrointest Endosc* 2018; 10(10): 274-282 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/274.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.274

INTRODUCTION

Caustic injury of the upper gastrointestinal tract remains one of the most challenging conditions presented to both gastroenterologists and surgical endoscopists. Endoscopy plays a major role in diagnosing and assessing the severity of caustic injury as well as guiding an appropriate treatment. Recently, computerized tomography (CT) scan of the chest and abdomen is increasingly used as complementary tool in the evaluation of caustic injury. Despite of advances in emerging technologies and treatments, severe morbidities and even death following the ingestion of caustic agents are evident in clinical practices thus suggesting the complexity of this condition.

Esophageal necrosis with subsequent perforation requiring emergency surgery may develop in the acute phase of caustic injury. Meanwhile, esophageal stricture (often being a complex stricture) is a late sequela of caustic injury which can be difficult to treat. Understanding fundamental knowledge of this condition will ensure the endoscopist to pursue the best course for the patient.

Although optimal management in the caustic injury of the esophagus remains rather inconclusive due to the lack of large epidemiologic studies and randomized clinical trials in the field, this narrative review summarizes current evidence on the role of endoscopy in the diagnosis and treatment of caustic injury of the esophagus. For the literature review, we used standard search strategies involving two online databases (PubMed and Scopus) using key words of caustic injury, corrosive ingestion, esophagus, endoscopy, diagnosis, treatment, dilatation, and surgery.

IMPACT OF CAUSTIC INJURY ON THE ESOPHAGUS

Caustic injury of the esophagus is a world-wide phenomenon. It was reported that in 2016 there were 176828 cases of caustic injury in the Unites States-accounting for 9.28% of all poisoning cases. The majority occurred in children with accidental ingestion[1]. Alkali ingestion is often seen in western countries, while acid ingestion is more common in Asian countries[2]. In Thailand, caustic ingestion involved 19.5% of poisoning cases and its incidence has been increasing[3]. Morbidity following caustic ingestion was high with a mortality rate of 8%. About one-third of patients with caustic ingestion eventually required surgery[4].

PATHOPHYSIOLOGY

Caustic injury occurs when substance with pH < 2 or pH > 12 is ingested. Due to the "liquefactive necrosis" of alkali substance, caustic injury from alkali can cause more damage to gastrointestinal tract than the "coagulative necrosis" of acid ingestion. Earlier report suggested that alkali usually destroyed the esophagus and acid mainly damaged the stomach[5]. However, later endoscopic study contradicted this notion by showing that among acid ingestion patients, esophageal injury was seen in 87.8% and gastric injury in 85.4% of the patients[6]. Recent evidence indicated that acid ingestion caused more injury to the stomach (31% *vs* 13%) while the incidence of esophageal injury was similar between acid and alkali ingestion[7]. Gastroesophageal reflux from impaired lower esophageal sphincter function[8] and loss of esophageal motility[9] are also results of a caustic damage to the esophagus. Meanwhile, caustic injury to the duodenum appeared to be infrequent and less severe owing to pyloric spasm.

Since a caustic injury to the esophagus usually starts within a few minutes after ingestion, any attempt to lavage or induce vomiting will cause the agent to reflux into the esophagus thus resulting in a further damage. A caustic injury to the esophagus can be divided into in 3 phases as following[10]: (1) Phase of acute necrosis and thrombosis occurs in 1-4 d after caustic ingestion; (2) phase of ulceration and granulation occurs in 3-12 d after caustic ingestion. During this period, mucosal sloughing, bacterial invasion and granulation formation are evident. The esophagus is in the most friable phase. Any manipulation such as endoscopic examination or dilatation should be done with great care; and (3) healing phase begins from 3 wk after injury. It usually takes 1-6 mo to complete wound healing. Attempt to perform surgery for stricture cases unamenable to dilatation should wait beyond this period.

PRE-ENDOSCOPIC TREATMENT

Stabilization of the patient is an ultimate goal during acute injury. Signs for airway injury *e.g.,* hoarseness, stridor and poor ventilation are diligently sought for and immediately treated (if any). An evaluation for laryngeal edema should be pursued by direct laryngoscopy. A careful history taking includes the substance ingested, the amount and time of ingestion, pre-hospital treatment and the cause of ingestion. In addition to airway management, other pre-endoscopic management includes volume resuscitation, nil per os (NPO), avoidance of emetics and neutralizing agents, no insertion of nasogastric tube, and administration of broad-spectrum intravenous antibiotics[11]. Chest and abdominal X-ray is often an initial investigation for evaluating an extension of injury. Psychiatry consultation should be done in case of suicidal attempt.

Table 1 Assessment of severity: endoscopic score and computerized tomography score

Grade	Endoscopic score[16]	score[21]
Ⅰ	Edema and hyperemia of the mucosa	No definite swelling of esophagus wall (< 3 mm, within normal limit)
Ⅱ	Ⅱa: Friability, hemorrhages, erosion, blisters, whitish membranes, exudates and superficial ulcerations Ⅱb: IIa with deep or circumferential ulceration	Edematous wall thickening (> 3 mm) without periesophageal soft tissue infiltration
Ⅲ	Ⅲa: Small scattered areas of necrosis Ⅲb: Extensive necrosis	Edematous wall thickening with periesophageal soft tissue infiltration plus well-demarcated tissue interface
Ⅳ	Perforation	Edematous wall thickening with periesophageal soft tissue infiltration plus blurring of tissue interface or localized fluid collection around the esophagus or the descending aorta

ENDOSCOPY IN THE ACUTE PHASE OF CAUSTIC INJURY

Since clinical signs such as drooling and oral burn are not accurate predictors for caustic injury to the esophagus[12,13], endoscopy is therefore considered as the most important investigation to diagnose of this injury. Early endoscopy is recommended because about 30% of patients with caustic ingestion will have no injury to the esophagus and can be discharged promptly. Endoscopy is usually done within 24-48 h after ingestion. However, many experts have recommended endoscopy as soon as possible[14,15] because delayed endoscopy was associated with prolonged hospital stay and increased hospital expense[16]. Although some reports confirm the safety of endoscopy performed up to 96 h after ingestion[17], initial endoscopy after 48 h of ingestion is not advised because the injured esophagus may enter the phase of ulceration and granulation - in which the esophagus becomes fragile and easily perforated[18]. Nevertheless, as long as the principles of gentle handling of the endoscopy are maintained, endoscopy after 48 h in selected cases might be possible.

In the past, endoscopists were not encouraged to pass the scope beyond circumferential burn due to the fear of esophageal perforation[19]. However, with advances in endoscopic examination and more skills in endoscopy, complete endoscopic evaluation beyond this point is possible with no complication[20]. Endoscopy is beneficial to confirm the followings: existence of injury, degree of injury, and area of injury - which could guide a treatment and predict a prognosis.

All adult patients (in which suicide attempt was the most common cause) should undergo endoscopy, but there is controversy regarding endoscopy in children (in which accidental ingestion was the most common cause)[21]. Most authors agreed that endoscopy should be done in children with signs of drooling, dysphagia, oral lesions, respiratory distress and intentional ingestion[22,23]. Beyond these scenarios, clinical observation may be appropriate.

Endoscopy is contraindicated in patients with a suspicion of gastrointestinal perforation, necrosis of oral cavity and compromised airway. Gentle handling and avoidance of air over-insufflation is always recommended. The comparison of modified endoscopic findings classified by Zargar *et al*[17] (Figure 1) and CT grading by Ryu *et al*[24] are shown in Table 1.

HOW DOES THE ENDOSCOPIC FINDINGS RELATE TO PROGNOSIS?

Classification and severity of caustic injury help predicting outcomes. Intentional ingestion, acid ingestion and high volume of ingestion were associated with a high grade of mucosal injury[4]. The patients with grade Ⅲb had longer hospital stay and higher rates of complication compared than those with grade Ⅲa[21]. However, a great variety of incidences in the degree of injury has been evident[4,7,11,12,18,21,25-28](Table 2). Discrepancy between inter-observers might reflect the difficulty to interpret the endoscopic findings especially when there was time lapsed before endoscopy. Treatment could be different according to the grading of severity as followings[11].

Grade Ⅰ (edema and erythema) or grade IIa (erosions and ulcers)

Since esophageal stricture will not occur in mild degree of injury, oral feeding can be resumed immediately and the patient can be discharged.

Grade Ⅱb (circumferential ulceration)

Oral feeding can start once the patient can swallow saliva - often after 24-48 h after ingestion. Stricture will ensue in 30%-70% of these patients[29]. Therefore, barium swallowing is recommended at 3 wk after ingestion to detect the stricture and early dilatation will be performed accordingly.

Grade Ⅲa (scattered areas of necrosis)

Risk of perforation cannot be neglected in these patients and esophageal stricture may occur more than 90%.

Grade Ⅲb (extensive necrosis)

Emergency surgery is recommended. However, some physicians might use CT scan to confirm true necrosis of the esophagus because endoscopists may be unable to distinguish between superficial necrosis and transmural necrosis.

Table 2 Variations in the degree of injury according to Zargar's classification from articles published after year 2000 in adult patients

Author	Year	Patients	Grade Ⅰ	Grade Ⅱ	Grade Ⅲ
Alipour Faz *et al*[4]	2017	313	42.5%	16.9%	20.1%
Ducoudray *et al*[7]	2016	n/a	n/a	n/a	39.7%
Cabral *et al*[11]	2012	315	12.7%	22.9%	29.2%
Chang *et al*[25]	2011	389	14.7%	39.3%	42.4%
Cheng *et al*[21]	2008	273	n/a	n/a	30%
Tohda *et al*[26]	2008	95	49.4%	26.3%	13.7%
Havanond *et al*[12]	2007	148	17%	41%	1%
Satar *et al*[27]	2004	37	67.5%	n/a	0%
Poley *et al*[18]	2004	179	40%	30%	30%
Rigo *et al*[28]	2002	210	32%	13%	6%

n/a: Not available.

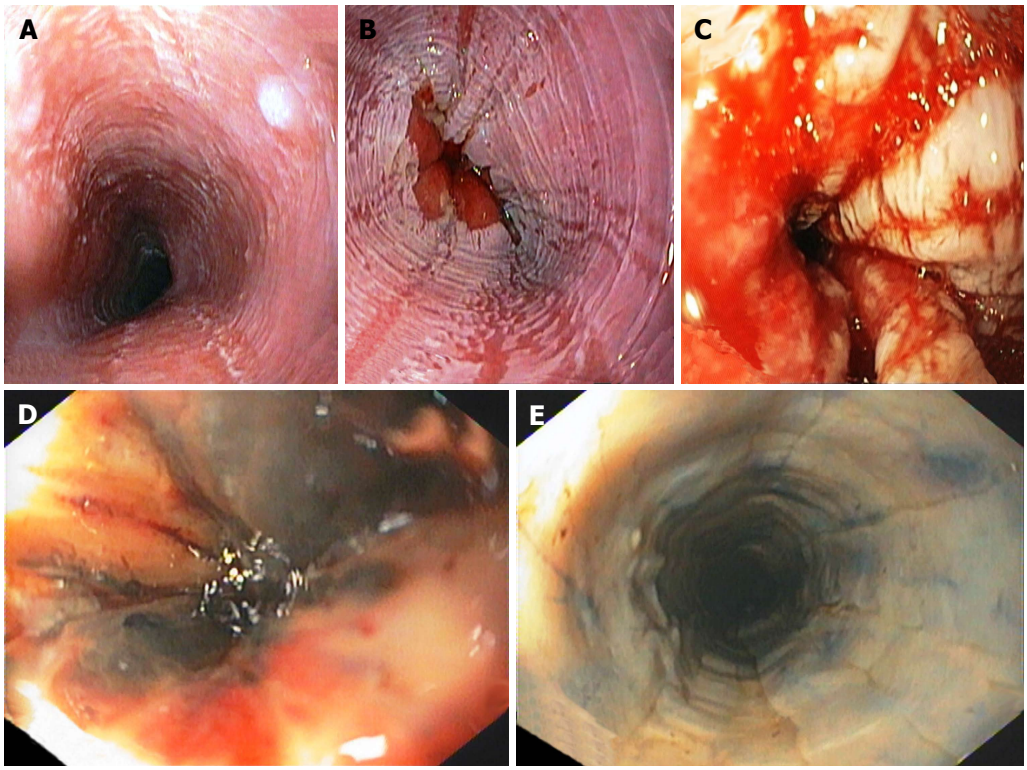

Figure 1 Modified Zargar's endoscopic classification of mucosal injury caused by ingestion of caustic substances. A: Edema and erythema; B: Erosions and ulcers; C: Circumferential ulceration; D: Scattered areas of esophageal necrosis; E: Extensive esophageal necrosis.

CT SCAN AND EUS IN THE EVALUATION OF CAUSTIC INJURY

It is evident that endoscopy is not always accurate in determining the extent of caustic injury (Figure 2). Depending on the endoscopic findings alone, grade Ⅲ injury would be over-estimated and unnecessary surgery was done in 15% of these patients[30]. Some authors showed that the accuracy in the diagnosis of grade Ⅱ and Ⅲ injury was 48% and 87%, respectively[31]. Recently, CT grading scores was developed in 2010 (Table 1) and shown to have a higher sensitivity and specificity than endoscopic score[24]. CT findings of transmural necrosis include esophageal wall blurring, peri-esophageal fat stranding and no enhancement of esophageal wall after intravenous contrast administrated. Recent studies showed that CT could prevent unnecessary esophagectomy in some patients with grade Ⅲb endoscopic score[32]. Although CT scan might underestimate the severity of caustic injury compared to endoscopy, it could provide further information about the involvement of adjacent organs *e.g.*, lung and pleural cavity[33]. Nevertheless, CT scan cannot replace endoscopy in the evaluation of caustic injury especial in those with mucosal damage[34]. The combination of endoscopy and CT scan has been utilized in clinical setting - in which surgery could only be performed in case with grade Ⅲb endoscopy and CT score[35].

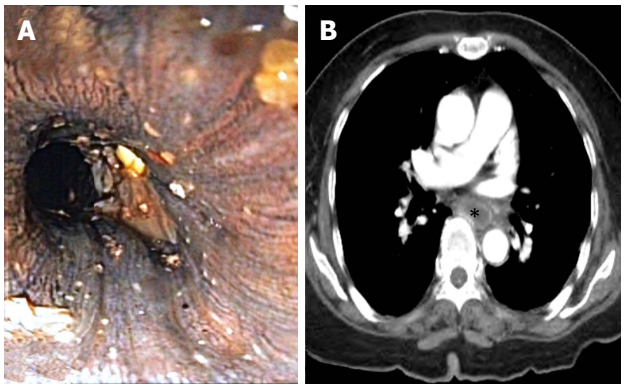

Figure 2 Endoscopic view suggested extensive mucosal necrosis of the esophagus -Grade Ⅲb modified Zargar's endoscopic classification, but CT scan revealed mucosal enhancement of the esophagus indicating tissue viability. A: Endoscopic view; B: Computerized tomography scan. Notably, esophageal lumen is marked with asterisk.

At present, combined use of endoscopy and CT scan, especially in case with grade Ⅲb endoscopic score, should help in the decision whether or not to operate.

Endoscopic ultrasonography (EUS) has some advantages over endoscopy and CT scan because it can delineate the layers of esophageal wall. If caustic injury is confined to submucosa in the EUS, the injured esophagus required a fewer sessions of esophageal dilatation than those with muscularis propria involvement[36]. Miniprobe EUS has been shown to predict stricture formation following caustic injury by visualizing the structure of esophageal wall[37]. However, the routine of EUS in clinical practice needs to be determined.

ENDOSCOPY IN THE LATE PHASE OF CAUSTIC INJURY

Endoscopy plays an important role in the treatment of caustic-related esophageal stricture. Caustic stricture is often complex and difficult to dilate[38]. Patients at risks for stricture were those with high endoscopic grade, ingestion of strong acid or alkali, leukocytosis and low thrombin ratio[39]. As acute inflammatory response to caustic agents lasts about 2 wk, early esophageal dilatation is usually done at 3 wk after caustic ingestion. After 8 wk, scar tissue is completely formed and the result of endoscopic dilatation is poor. Since good nutritional status is strongly related to a successful dilatation of esophageal stricture[40], early feeding *via* jejunostomy should start as soon as patients are clinically stable - especially in those with a significant damage in the esophagus and the stomach.

Practically, barium swallowing is done at 2-3 wk after caustic ingestion. Barium swallowing will provide crucial and relevant information on the stricture - which could determine the safety and success of endoscopic dilatation. This information includes:

(1) location and length of the stricture; (2) morphology of the stricture: tortuosity, angulation; (3) nature of the stricture: simple or complex; (4) complications of the stricture: concealed perforation, diverticulum; and (5) configuration of the stomach: any accompanying gastric stricture.

Esophageal dilatation can be done using various types of dilators. It can be performed under the combination endoscopy and fluoroscopy or endoscopy alone[41]. Commonly used esophageal dilatators are followings(Figure 3).

Bougie dilator (Maloney-Hurst dilator)

This dilator is easy to use but has no channel to insert guide-wire. It is suitable for short and straight stricture.

Wire-guided Polyvinyl dilator (Savary-Gilliard dilator)

This dilator passes through the stricture *via* guide-wire under fluoroscopy. It is appropriate for tortuous, angulated and long stricture. Sensation of resistance during dilatation can be noted on this dilator thus resulting in protecting against over-dilatation.

Through-the-scope balloon dilator (CRE balloon dilator)

This instrument can be used through-the-scope. It can reach area where Savary dilator cannot access. However, there is no sensation of resistance if over-dilatation occurs.

CRE balloon dilators achieve its dilatation effect by radial force while Savary and Maloney dilators exert its action *via* both radial and longitudinal forces. Although the mechanisms are different, all dilators seem to have comparable success rate and rate of perforation of 0.1%-0.4%[42]. Concerning the safety of an instrument, balloon dilator is preferred over Bougie dilator in children[43]. Techniques of esophageal dilatation are noted in Table 3.

In order to prevent the over-dilatation of esophageal stricture, the rule of 3 is recommended as "never dilate more than 3 dilators of progressively increasing diameter after considerable resistance is encountered"[44]. Although some retrospective study showed that non-adherence to this rule did not increase the risk of esophageal perforation[45], we believe that the rule remains useful as a landmark during dilatation and a preventive measure of over-dilatation. Success rate of esophageal dilatation varied from 25% to 95% depending on the severity of caustic stricture[46-48].

ENDOSCOPY IN REFRACTORY CAUSTIC STRICTURE OF THE ESOPHAGUS

Caustic stricture that could not be dilated to 14 mm over 5 sessions done with bi-week interval is defined as refractory stricture[49]. For refractory stricture, various modalities are advocated including electrocision, intralesional steroid injection, mitomycin-C injection, and esophageal stent.

Electrocision

Electrocautery could be applied to caustic stricture as

Table 3 Techniques of esophageal dilatation

Early dilate (usually starting from 3 wk after caustic ingestion)
Use appropriate type and size of dilator
Maintain a dilator in lumen of the esophagus while dilating
Concern the rule of 3: Never dilate more than 3 dilators of progressively increasing diameter after considerable resistance is encountered
Weekly or bi-weekly dilate to obtain luminal competency at 40 Fr
Dilate per scheduled, not on demand
If chest pain occurs after dilatation, esophageal perforation must be rule out using contrast esophagography

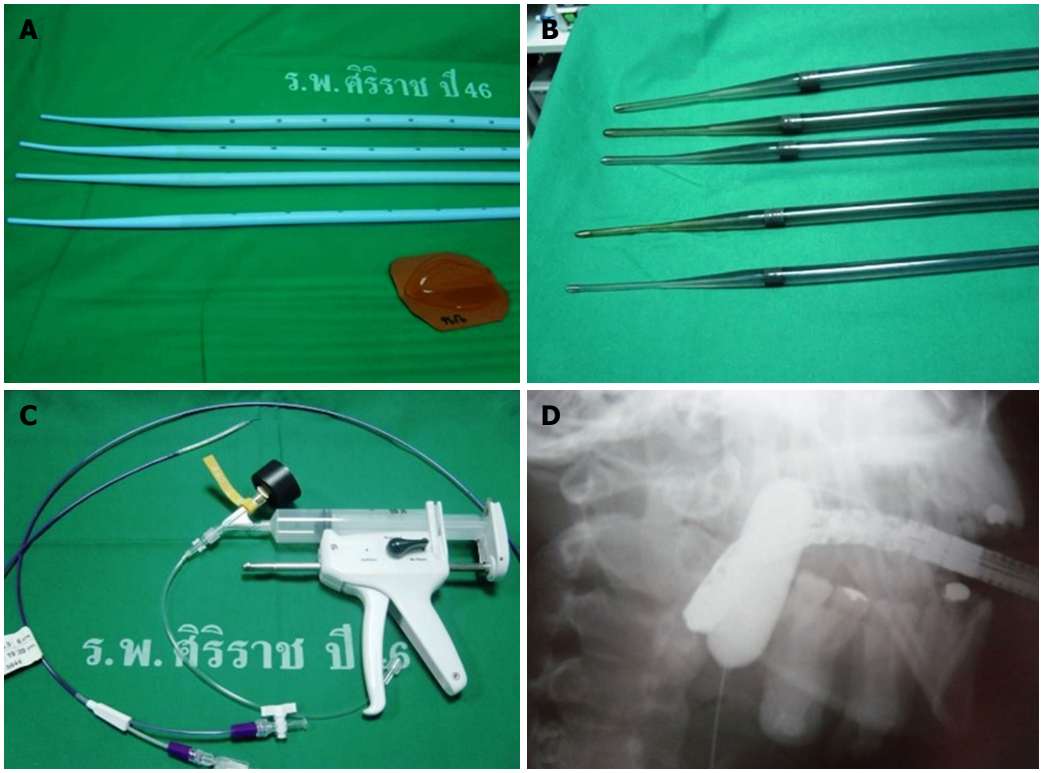

Figure 3 Various types of dilator. A: Maloney-Hurst dilator; B: Savary-Gilliard dilator; C: Balloon dilator; D: Balloon dilator during dilatation seen with fluoroscopy.

it has been used in the treatment of Schatzki's ring and anastomotic stricture with good results[50]. Multiple longitudinal incisions are made with needle knife through working channel of the endoscopy until the rim of the stenosis disappears. This maneuver proves to be a useful adjunct in esophageal dilatation.

Intralesional steroid injection

In this method, prior to bougie dilatation, triamcinolone acetonide (40 mg/mL) 1 mL is diluted to 2 mL and injected at the stricture site in 4 quadrants. Combination of steroid injection and bougie dilatation could achieve more dilatation, improve dysphagia and reduce dilatation sessions[51].

Mitomycin-C injection

Injection of mitomycin-C into the stricture site was shown to improve dysphagia score and easy passage of dilators[52-54] because mitomycin-C inhibited fibroblast proliferation and scar formation without interfering wound healing[55]. A randomized controlled trial showed a reduction in dilatation sessions if applying mitomycin-C during dilatation[56]. Mitomycin-C is beneficial in difficult or complex caustic stricture and can be combined with other modalities such as electrocision and esophageal stent[57].

Esophageal stent

Caustic stricture resistant to dilatation can be treated with esophageal stent insertion. Self-expandable plastic stent (SEPS) or fully-covered self-expandable metallic stent (FCSEMS) and recently, biodegradable stent are available. Practically, SEPS and FCSEMS are kept in place for 6 wk and should be removed before 12 wk. All types of esophageal stent have comparable efficacy but biodegradable stent has an advantage in non-requirement of stent removal. The clinical success of stent application in caustic stricture (*i.e.*, free of dysphagia) was 33% with a migration rate of 40%[58,59]. Since its clinical success is about one-third and not last-longing, esophageal stent is considered as a last resource in the treatment of caustic injury.

INDICATIONS FOR SURGERY IN CAUSTIC-INDUCED ESOPHAGEAL STRICUTRE

Esophageal dilatation for caustic-induced stricture injury has lower success rate than esophageal stricture related to other etiologies[60]. Esophageal replacement is considered in patients who fail endoscopic therapy. Up to 50%-70% of patients with caustic stricture required surgery[46,61]. Stomach is used as a conduit if possible because it has less morbidity and mortality than colonic interposition[62]. If colonic interposition is required, transverso-splenic to ileocolic segment with blood supply *via* left colic artery provided excellent function in 75% of the patients[63]. In general, surgery should wait 6 mo after caustic ingestion for stabilizing patient, improving nutritional status, and allowing enough time to full attempt of endoscopic therapy.

THE ROLE OF ENDOSCOPY IN THE LONG TERM FOLLOW-UP OF ESOPHAGEAL CAUSTIC INJURY

Since caustic injury of the esophagus has been associated with 1000-fold increased risk of esophageal carcinoma[61], patients with high-graded caustic injury (especially that with esophageal stricture) should undergo endoscopic surveillance. The incidence of caustic-associated esophageal cancer ranges from 0%-30% and bypass surgery seems to have no influence on cancer development[64]. The time interval between caustic injury and malignant transformation of the esophagus was reported to be several decades[65]. As a result, endoscopic surveillance of the injured esophagus should start at about 15-20 years after an injury and it should be done every 2 or 3 years[66].

CONCLUSION

Endoscopy plays a crucial role in the diagnosis, assessment of severity, treatment and surveillance in patients with caustic injury of the esophagus. Meanwhile, CT scan of chest and abdomen has been increasingly used to improve accuracy in the diagnosis and severity assessment in difficult cases of esophageal caustic injury. Choice of endoscopic management and surveillance are considered mainly based on the grading of mucosal severity. Patients with high-graded mucosal injury are associated with increased risk of caustic-induced esophageal stricture which could be difficult to dilate due to its complex anatomy and extensive fibrosis. Better techniques or instruments for endoscopic dilation need to be developed to overcome this problem. Since caustic injury significantly increased risk of esophageal carcinoma, scheduled endoscopic surveillance every 2 or 3 years should perform at 15-20 years after an injury-especially in individuals with high-graded mucosal injury or those with esophageal stricture. Due to the complex nature of disease, caustic injury of the esophagus remains one of the most challenging clinical conditions presented to endoscopists.

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P- Reviewer: Durand L, Ntanasis-Stathopoulos I **S- Editor**: Cui LJ
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2018 October 16; 10(10): 283-293

DOI: 10.4253/wjge.v10.i10.283

ISSN 1948-5190 (online)

MINIREVIEWS

Linear endoscopic ultrasound evaluation of hepatic veins

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Author contributions: Sharma M wrote the manuscript; Somani P, Rameshbabu CS edited the manuscript; Sharma M, Somani P, Rameshbabu CS designed the study.

Conflict-of-interest statement: Authors declare no conflict of interests for this article

Manuscript source: Invited manuscript

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Received: June 7, 2018
Peer-review started: June 7, 2018
First decision: June 15, 2018
Revised: July 30, 2018
Accepted: August 12, 2018
Article in press: August 13, 2018
Published online: October 16, 2018

Abstract

Liver resection surgery can be associated with significant perioperative mortality and morbidity. Extensive knowledge of the vascular anatomy is essential for successful, uncomplicated liver surgeries. Various imaging techniques like multidetector computed tomographic and magnetic resonance angiography are used to provide information about hepatic vasculature. Linear endoscopic ultrasound (EUS) can offer a detailed evaluation of hepatic veins, help in assessment of liver segments and can offer a possible route for EUS guided vascular endotherapy involving hepatic veins. A standard technique for visualization of hepatic veins by linear EUS has not been described. This review paper describes the normal EUS anatomy of hepatic veins and a standard technique for visualization of hepatic veins from four stations. With practice an imaging of all the hepatic veins is possible from four stations. The imaging from fundus of stomach is the easiest and most convenient method of imaging of hepatic veins. EUS of hepatic vein and the tributaries is an operator dependent technique and in expert hands may give a mapping comparable to computed tomographic and magnetic resonance imaging. EUS of hepatic veins can help in identification of individual sectors and segments of liver. EUS guided interventions involving hepatic veins may require approach from different stations.

Key words: Endoscopic ultrasound; Hepatic vein; Portal vein; Liver segments; Caudate lobe; Inferior vena cava; Liver; Cantlie line; Falciform ligament; Gall bladder

Core tip: A standard technique for hepatic veins imaging by linear endoscopic ultrasound (EUS) has not been described. EUS of hepatic veins can help in identification of individual sectors and segments of liver. This review paper describes the normal EUS anatomy of hepatic veins and a standard technique for visualization of hepatic veins from four stations.

Sharma M, Somani P, Rameshbabu CS. Linear endoscopic ultrasound evaluation of hepatic veins. *World J Gastrointest Endosc* 2018; 10(10): 283-293 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/283.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.283

INTRODUCTION

Liver resection surgery is associated with significant perioperative mortality and morbidity[1]. Despite refinements in hepatic surgical techniques, vascular complications still occur. A detailed knowledge of the vascular anatomy and pre-surgical planning of vascular anastomosis on a vessel-to-vessel basis is essential for successful, uncomplicated liver surgeries[2-5]. A wide variety of imaging strategies are used to provide comprehensive preprocedural information about hepatic angioarchitecture[6]. Currently multidetector computed tomographic (CT) and magnetic resonance angiography are complementary modalities of hepatic angioarchitecture evaluation[7]. Ultrasound offers the advantage of Doppler assessment[8,9]. Despite comprehensive evaluation many smaller vessels may not be picked up, however from a surgical point of view these smaller vessels are insignificant and are tied up during surgery. The identification of these smaller vessels and specifically accessory veins of liver is sometimes important as they may drain a complete segment of liver. Separate segmental venous anastomosis is required for such cases to maintain sufficient hepatic venous drainage and to prevent postoperative complications resulting from the venous obstruction. An adequate maintenance of segmental hepatic venous drainage is also important as there is no adequate venovenous shunt between hepatic venous systems[10,11]. Linear endoscopic ultrasound (EUS) can offer a detailed evaluation of hepatic veins, help in assessment of liver segments and can offer a possible route for EUS guided vascular endotherapy involving hepatic veins. A standard technique for visualization of hepatic veins by linear EUS has not been described. This article describes the normal EUS anatomy of hepatic veins.

APPLIED ANATOMY: LIVER LOBES, SECTORS AND HEPATIC VEINS

The anatomical classification of the liver, which divides the right and left lobe by the attachment of the falciform ligament is no longer accepted in routine terminology. The true physiological classification divides right and left hemi-liver by an imaginary line of Cantlie. Typically, the Cantlie's line is 1 cm to the right of the middle hepatic vein (MHV), and corresponds to an important surgical plane in the sagittal axis that extends craniocaudally from the medial aspect of the gallbladder fossa to the left margin of inferior vena cava (IVC) (Figure 1A). Posteroinferiorly this line passes from gallbladder fossa to the main bifurcation of hepatic pedicle (portal triad) and then to retrohepatic IVC.

The hepatic veins are thin-walled anechoic vessels which do not have any valves, originate from the core (central) vein of the liver lobule and drain blood toward the IVC. The hepatic veins can be segregated into three major veins (right, middle and left) and many accessory veins or short hepatic veins. The three major hepatic veins are 6 to 15 mm in diameter, have no course outside liver and open directly into the supra hepatic part of IVC in the bare area of the liver (Figure 1B). The major veins are intersegmental in their course and divide the liver into four sectors; right anterior, right posterior, left medial and left lateral. The divisions separating the sectors are called portal fissures, which do not correspond to any superficially visible clefts but within each of which runs a hepatic vein. The right hepatic vein lies in the right portal fissure and separates the right hemi liver into anterior and posterior sectors. The right hepatic vein is the longest vein, passes through the segment I and lies parallel to the gallbladder fossa. The left hepatic vein (LHV) lies in the left portal fissure which is very close to the course of ligamentum venosum and separates the left hemi liver into medial and lateral sectors. The MHV lies in the middle portal fissure and separates the anterior division of right liver from medial division of left liver (Figure 1A). The accessory veins join the retro or intrahepatic part of IVC and are usually smaller in diameter (Figure 1B). The basic organisation of the segments and sectors of liver in relationship with hepatic vein tributaries is shown in Figure 2.

TECHNIQUES OF EVALUATION

The images given in this pictorial essay are taken by Pentax UTK 3870 UT from cases undergoing EUS examination. The imaging of hepatic veins is usually aided by proper identification of the IVC and the gallbladder both of which are discussed as important home bases for imaging of hepatic veins.

Imaging of IVC

IVC can be visualized from different positions during EUS. The appearance of IVC may vary from rounded to an elongated axis depending on the axis of imaging and the angulation of the probe in these positions (Figures 3-7). It is usually possible to image the entire length (approximately 6 to 8 cm) of intrahepatic/retrohepatic part of IVC in a single frame at 1 to 3 cm distance from the probe in an axis parallel to the probe near the esophagogastric junction. In this position the surface closer to the probe corresponds to the posterior surface of IVC and the surface away from the probe corresponds to the anterior surface of IVC (Figure 8). The position and course of each of the hepatic vein is usually best assessed from the abdominal part of esophagus. Slight clockwise or anticlockwise rotation can trace the lateral surfaces

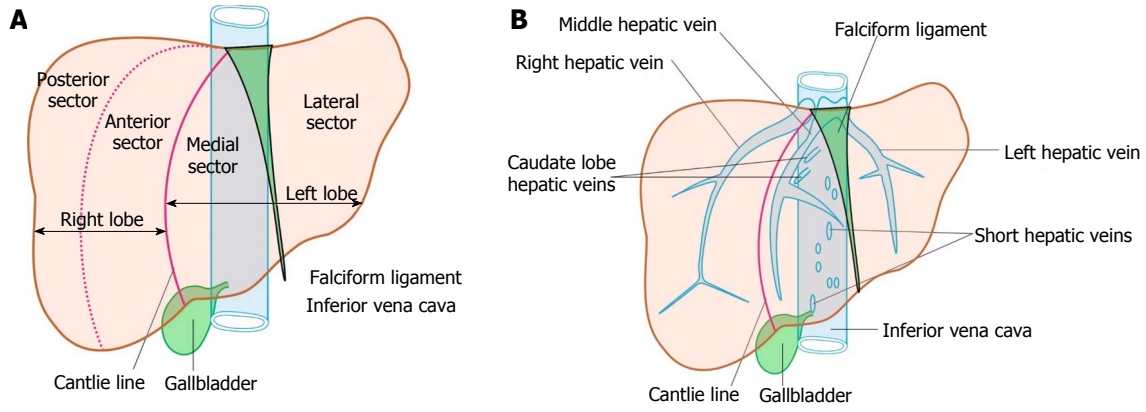

Figure 1 Anatomy of liver. A: The four sectors of liver, *i.e.*, right anterior, right posterior, left medial and left lateral; B: The three major veins, emerge from the posterior surface of the liver and open immediately into the supra hepatic part of inferior vena cava (IVC) just before it pierces the diaphragm. Short hepatic/accessory veins drain into lower part of IVC. The accessory veins and the caudate lobe veins join the anterior and lateral aspect of IVC.

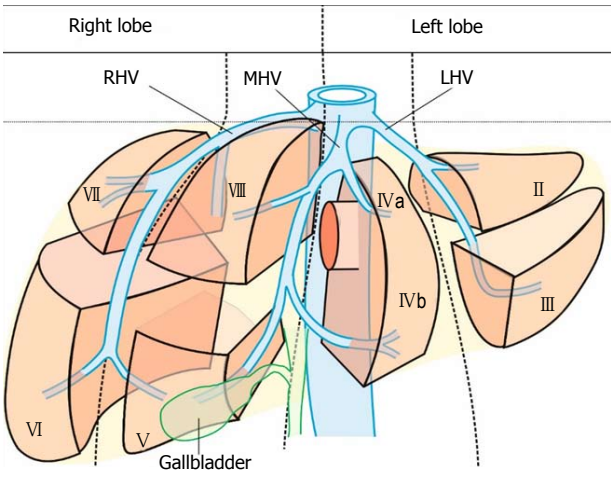

Figure 2 The segments and sectors of liver and their relationship with hepatic vein tributaries. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein.

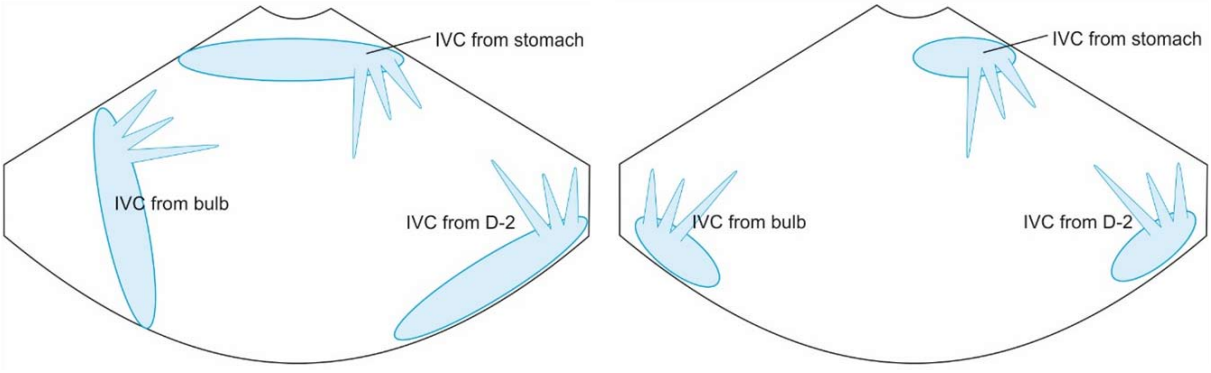

Figure 3 The appearance of inferior vena cava from three stations in a rounded or elongated axis.

of the IVC. The supra hepatic, or retro hepatic course of IVC can be followed for assessment of hepatic veins which join the anterior or lateral surface of IVC. No vein joins the posterior surface of IVC. During imaging from abdominal part of esophagus and stomach the spiral course of IVC in the liver is easily traced from above downwards from an anteriorly placed position of the IVC near the right atrium to a posteriorly placed position of the IVC in abdomen (Figures 4, 5, 8 and 9). The imaging of IVC and the hepatic veins is also possible from duodenal bulb and descending duodenum but the longer distance of hepatic veins and IVC from the bulb

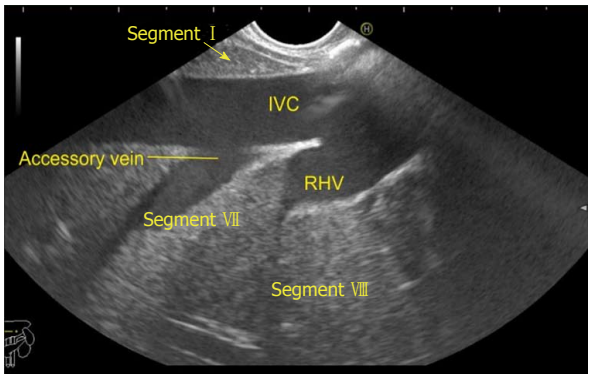

Figure 4 Inferior vena cava running parallel to the probe in a long axis from abdominal part of esophagus. RHV: Right hepatic vein; IVC: Inferior vena cava.

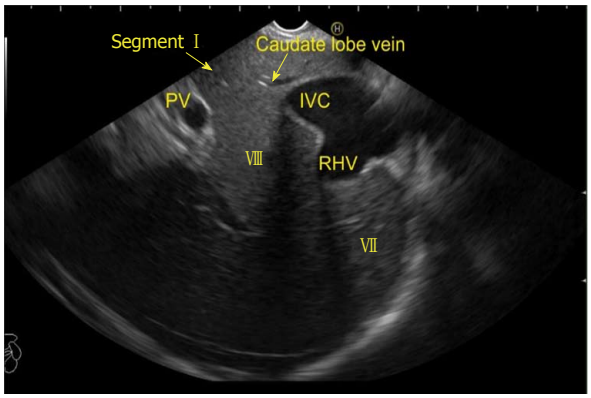

Figure 5 This figure shows inferior vena cava running parallel to the probe in a long axis. In this image slight up angulation of the probe shows inferior vena cava in a more oval axis. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

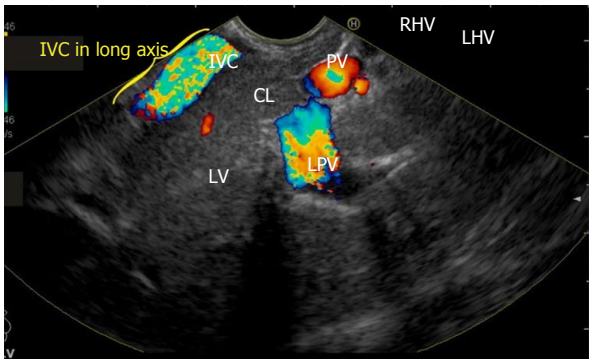

Figure 6 This figure shows inferior vena cava running from 7 o'clock position to 11 o'clock position on the far side of the screen in a long axis from the duodenal bulb. PV: Portal vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava; CL: Caudate lobe; LPV: Left portal vein.

and descending duodenum may make it technically difficult to acquire similar amount of information (Figures 6 and 7).

Imaging of gallbladder

The gallbladder lies in a shallow fossa on the down sloping visceral surface of liver and can be visualized from

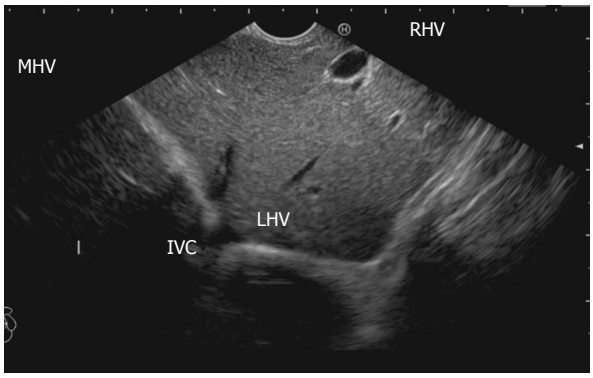

Figure 7 This figure shows inferior vena cava in a rounded axis from duodenal bulb. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

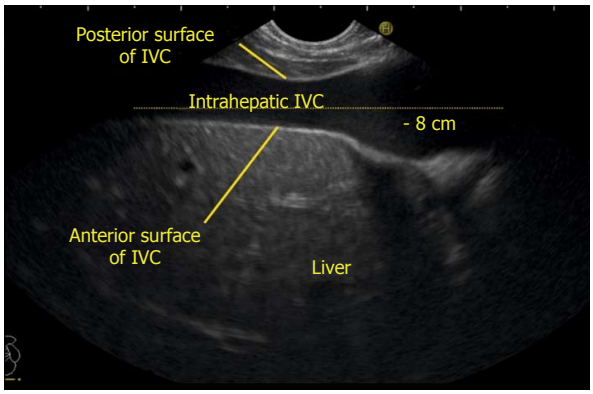

Figure 8 During imaging from the abdominal part of esophagus, the anterior surface of inferior vena cava is always found in close contact with the liver parenchyma whereas the posterior or lateral surface of the inferior vena cava is variably covered. IVC: Inferior vena cava.

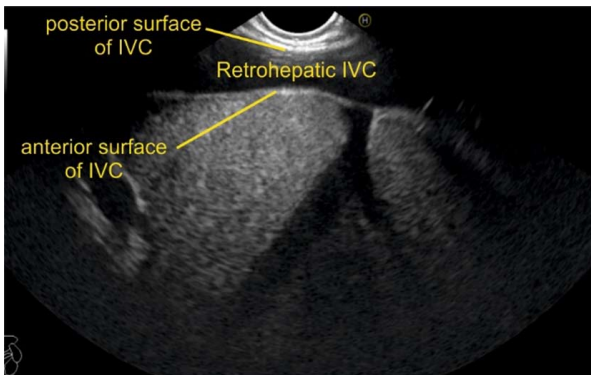

Figure 9 If the inferior vena cava is surrounded on all sides by liver parenchyma it is called as intrahepatic, if it is surrounded only anteriorly or anterolaterally it is called as retrohepatic. In this case, right hepatic vein is seen joining the retrohepatic part of inferior vena cava. IVC: Inferior vena cava.

the stomach, the duodenal bulb and from the descending part of duodenum. It is located near the right end of porta hepatis, its neck is highest, its fundus lowest. The location of gallbladder helps in following the course of hepatic vein; the right hepatic vein runs parallel to the upper surface of gallbladder (Figure 10), the MHV runs towards the neck of gallbladder (Figure 10) and the LHV

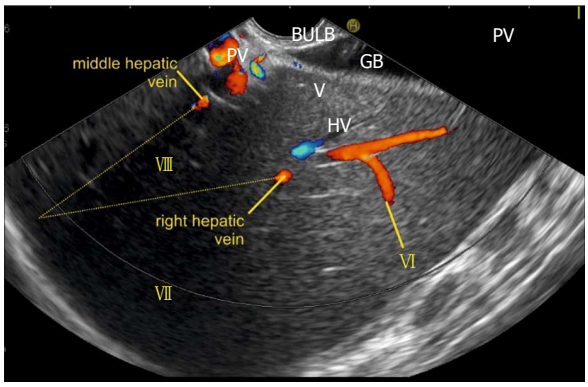

Figure 10 This image from duodenal bulb shows the right and middle hepatic vein. The right hepatic vein goes parallel to the surface of gallbladder and the middle hepatic vein goes towards the neck of gallbladder. GB: Gall bladder.

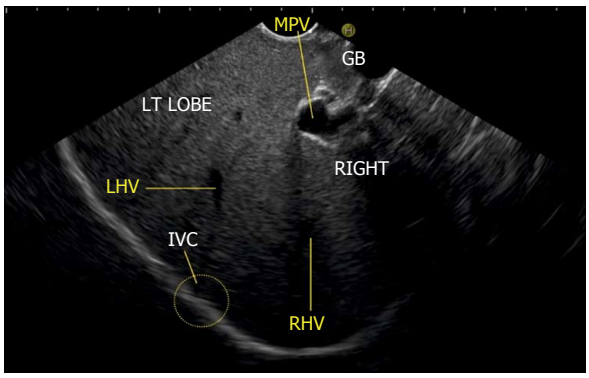

Figure 11 The inferior vena cava is not seen in this image but rotation of the scope shows the approximate area of inferior vena cava (yellow circle) where the left and right hepatic veins merge into inferior vena cava. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

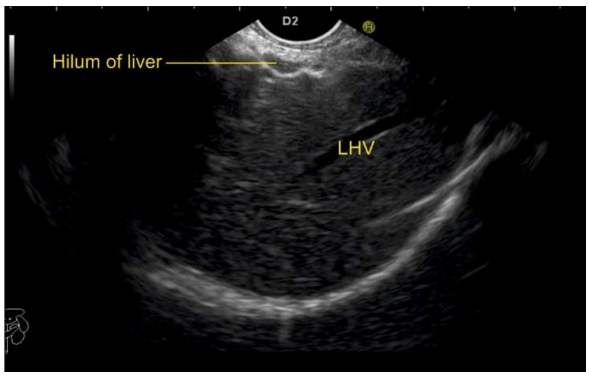

Figure 12 While imaging through the left lobe, the left hepatic vein is seen as a long vascular channel coursing towards the right side of the image into inferior vena cava which is usually seen in a rounded shape in a transverse axis. LHV: Left hepatic vein.

runs away from the neck of the gallbladder (Figures 11 and 12).

EVALUATION OF HEPATIC VEINS

The course of hepatic veins and the hepatic vein branches is described from four stations: the abdominal part of esophagus, the fundus of stomach, the duodenal bulb and the descending duodenum (Figure 13). The imaging from each station may be done in following steps: (1) Demarcation of right and left lobe is done by following the course of MHV. The course of left and right hepatic vein helps in identification of the four sectors (Figure 14); (2) Further subdivision of the sectors into independent liver segments is possible by following the tributary free part of each hepatic vein and tracing the direction and path of travel of the tributaries (Figure 15); and (3) The location and side of appearance of 1st major tributary of each hepatic vein is helpful for segmental identification (Figures 15-18).

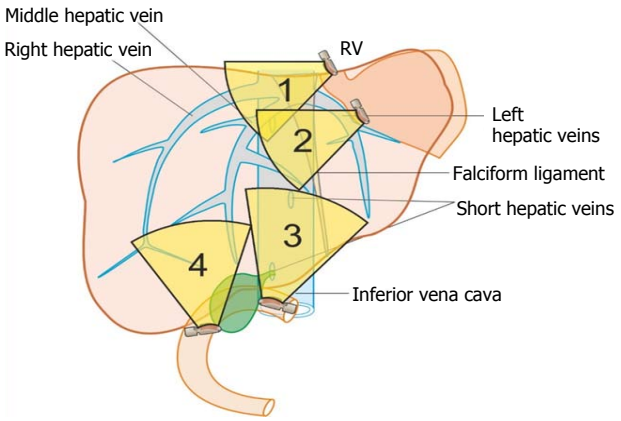

Figure 13 The imaging of hepatic veins can be done from four stations: the abdominal part of esophagus, the stomach, the duodenal bulb and the 2nd part of duodenum.

Evaluation from abdominal part of esophagus

The abdominal part of esophagus lies very close to the entry point of left and MHV into the suprahepatic part of IVC. Initially the LHV is identified in an open position to the left (Figures 12 and 14A). The course of LHV divides the left lateral and left medial sector (Figure 14A). Slight clockwise rotation traces the joining of MHV at an angle of about 60° with the IVC (Figures 14B and 16). The presence of MHV divides the left medial (IVa) from right anterior sector (Figures 14B and 16). On further rotation, the right hepatic vein is seen, which divides the right anterior from right posterior sector (Figures 14C and 17). Usually in this position the merger of right hepatic vein is seen when the IVC is seen in an axis parallel to the probe (Figure 17). With a single movement of clockwise rotation from abdominal part of esophagus, the three hepatic veins can be identified within the portal fissures and the four sectors can be separated according to the order of appearance of hepatic veins (Figure 13).

Evaluation from the stomach

A EUS examination of most of the liver lobe, sectors and hepatic veins is possible from the visceral surface of liver which is in contact with stomach and forms the gastric impression on the under surface of liver (Figure

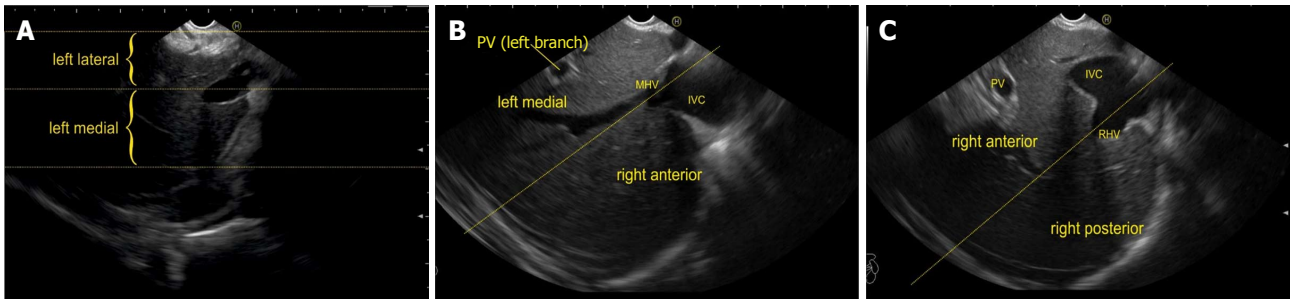

Figure 14 The images from abdominal part of esophagus shows presence of left (A), middle (B), and right hepatic vein (C) dividing the liver into four sectors. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

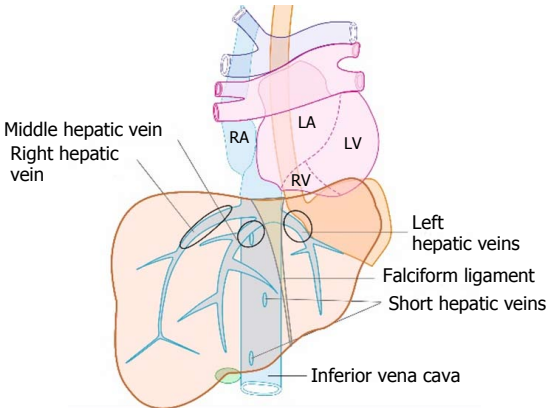

Figure 15 The tributary free part of each hepatic vein is shown.

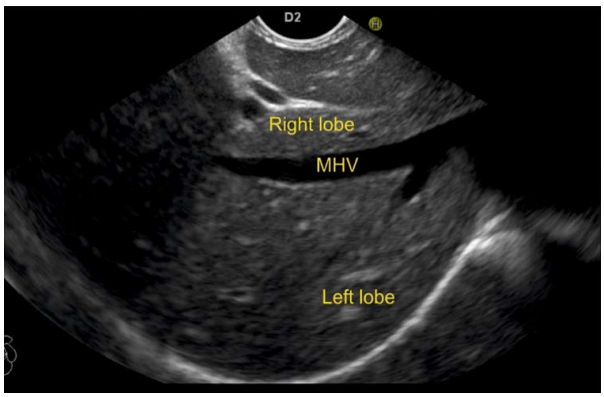

Figure 16 The middle hepatic vein has got tributaries on the right and the left side. The right side tributaries drain segment Ⅷ and segment Ⅴ. The left side tributaries drain segment Ⅳ. MHV: Middle hepatic vein.

19A and B). An open position to left places the tip of the transducer close to left lateral sector of liver in stomach. A clockwise rotation from an open position to the left brings into view the umbilical part of left branch of portal vein within the umbilical fissure which lies close to left edge of transverse fissure. Further clockwise rotation traces the transverse fissure from the left edge of the fissure to the right edge and moves the beam of probe from the left lateral sector to left medial sector (Figure 20). On continued rotation the beam moves towards the right anterior sector where the gallbladder

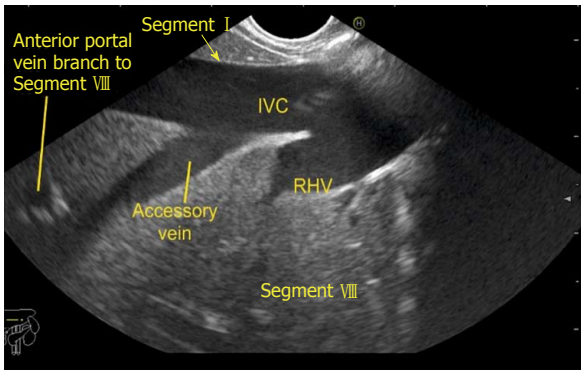

Figure 17 The right hepatic vein is seen joining at an angle of around 60°. The segment Ⅷ is seen between hepatic vein and IVC. RHV: Right hepatic vein; IVC: Inferior vena cava.

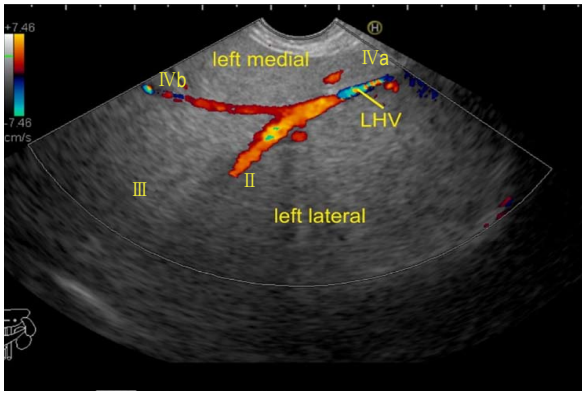

Figure 18 The left hepatic vein is seen running parallel to the probe. The segment Ⅱ, Ⅲ, Ⅳa and Ⅳb veins are seen. In this case the imaging is done from the visceral surface of the liver and from an area close to the antrum and body. Hence, the segment Ⅳb appears closer than segment Ⅲ. LHV: Left hepatic vein.

is seen (Figure 21).

Evaluation from the duodenal bulb

Imaging from duodenal bulb requires positioning of the scope in the duodenal bulb where clockwise and anticlockwise rotation results in appearance of left and right lobe (Figure 22). The presence of MHV is seen moving towards the neck of gall bladder and this divides the liver into right and left lobe (Figure 23).

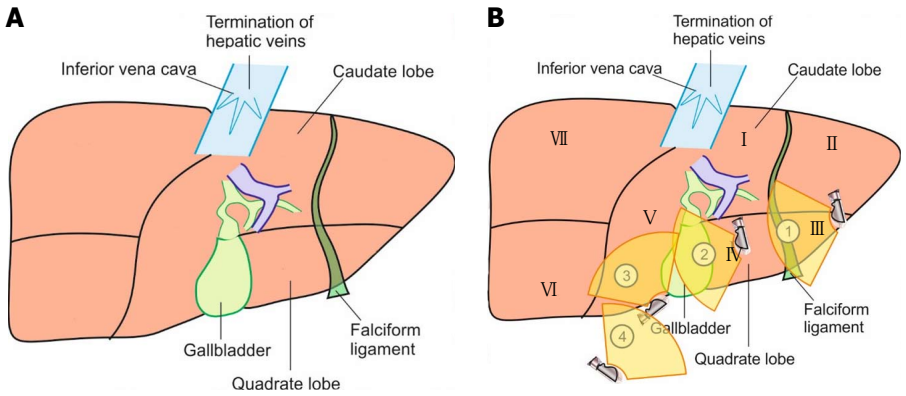

Figure 19 Visceral surface of liver. A: The visceral surface of the liver is shown. All the segments of liver except segment VIII are related to the visceral surface of the liver; B: The imaging from visceral surface of liver can be done from four positions.

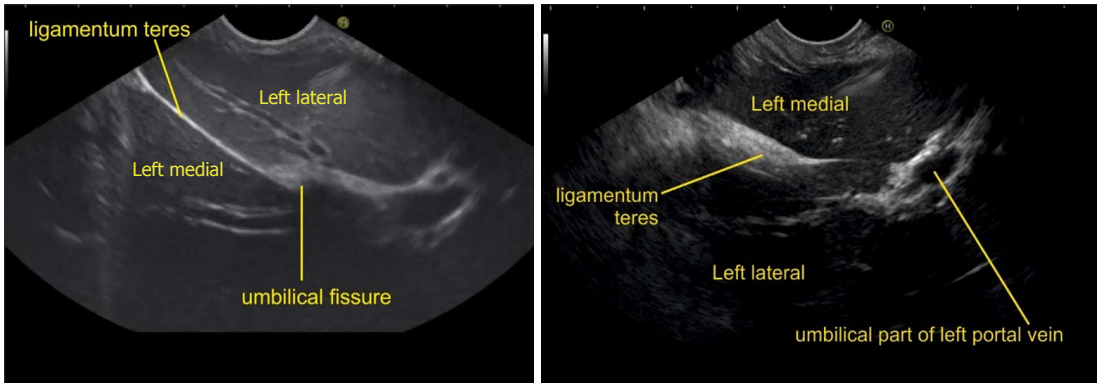

Figure 20 Imaging from visceral surface of liver shows the left lateral and left medial segment below the level of umbilical fissure separated by ligamentum teres.

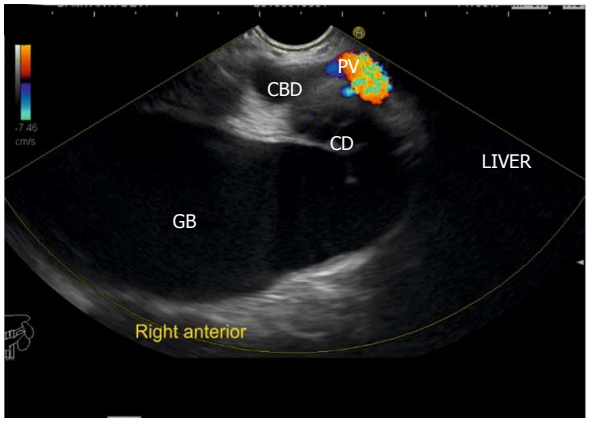

Figure 21 This image shows right anterior sector from stomach. CBD: Common bile duct; CD: Cystic duct; GB: Gallbladder.

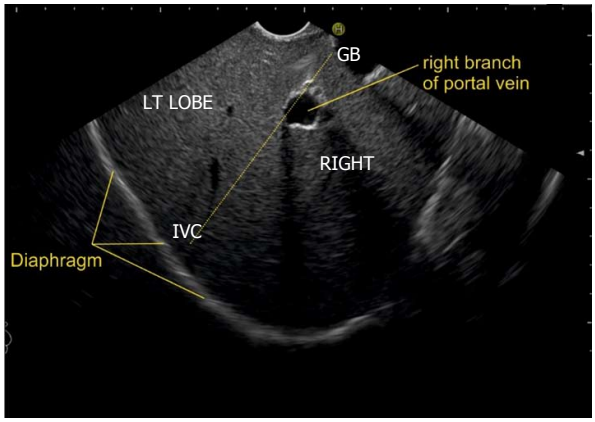

Figure 22 This image from duodenal bulb shows an imaginary line (dotted yellow line) going from inferior vena cava towards the gallbladder. This line divides the right and left lobe of liver. The right branch of portal vein is seen as a rounded structure within the liver parenchyma in the path of this line. GB: Gallbladder; IVC: Inferior vena cava.

Further division into sectors is possible by clockwise rotation to visualize the left lobe (Figure 24) and anticlockwise rotation to visualize the right lobe (Figure 25). Imaging from the duodenal bulb usually visualizes the gallbladder neck near the liver hilum at 12 o'clock position, fundus at 3 o'clock position (Figures 23 and 25) and in this position the IVC is seen moving from 6 to 9 o'clock positions (Figure 24). A clockwise rotation moves the beam towards the duodenum and towards the retrorenal part of IVC whereas as an anticlockwise rotation traces the IVC towards the right lobe of liver.

Evaluation from the descending duodenum

The evaluation of the hepatic veins from descending duodenum is possible by extreme anti-clockwise rotation

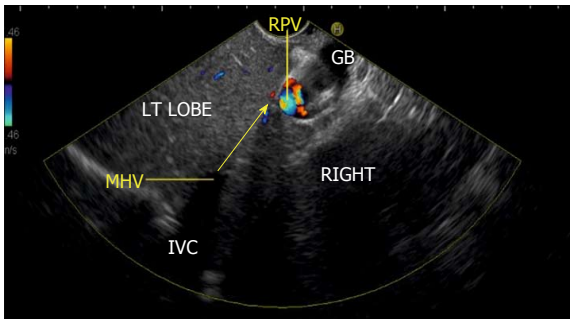

Figure 23 This image shows that the middle hepatic vein going towards the neck of gallbladder (yellow arrow). MHV: Middle hepatic vein; GB: Gallbladder; IVC: Inferior vena cava; RPV: Right portal vein.

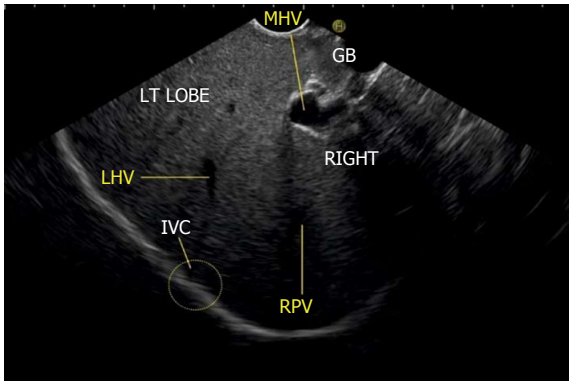

Figure 24 This image shows the course of left hepatic vein on clockwise rotation in duodenal bulb. MHV: Middle hepatic vein; GB: Gallbladder; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

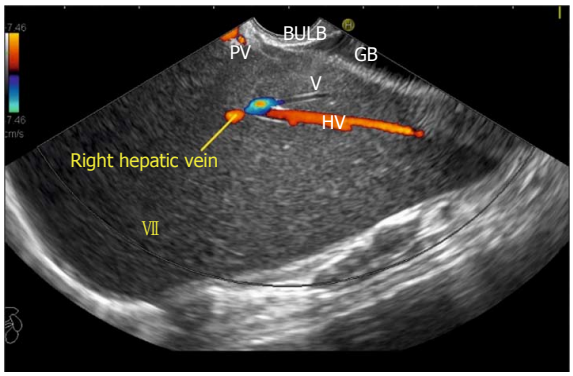

Figure 25 Imaging from duodenal bulb with anticlockwise rotation to visualize the right lobe. The middle hepatic vein is seen coursing from the neck of the gallbladder and the right hepatic vein is seen coursing parallel to the upper surface of gallbladder. An imaginary line can be drawn back to the approximate position of merger into inferior vena cava which is not seen in this frame.

coupled with upwards angulation to prevent the slipping of the scope back into the stomach. During this rotation, the beam moves traces the IVC from behind the kidney towards the heart and sequentially rotates towards the axis of imaging across the right lobe of the liver, the gallbladder fossa and the left lobe of liver. In this position the IVC gradually moves from 9 o'clock position towards 4 o'clock position (Figure 26). During this rotation, the MHV (Figure 27), the RHV (Figure 28) and the LHV (Figure 29) appear one by one and help in identification of all the sectors of liver.

Evaluation of short hepatic/accessory veins

The accessory veins have significant variations in their number and size and the size may be larger, smaller or of the same size as the main hepatic veins. Larger size accessory veins usually provide independent and complete drainage of blood from a complete liver segment[11]. A universal classification of accessory veins is not given in literature and a simple description of accessory veins may mention all veins joining the IVC caudal to the main veins as right, middle or left inferior hepatic veins. Sometimes the accessory veins are classified into two groups according to the side that enter into IVC. The left side veins are called caudal hepatic veins, while the right sided veins are referred to as inferior right hepatic veins. On EUS the evaluation of the anterior and lateral wall of IVC below the joining of main hepatic vein is done in a craniocaudal axis (no vein joins the posterior aspect of IVC) for assessment of accessory veins (Figures 30-32). The number and diameter of hepatic veins joining IVC can be counted. The caudate lobe venous drainage is independent and occurs directly by two small fairly constant veins that enter the left side of IVC (Figure 5). In cases of liver donor, the caudate lobe usually remains in the donor because it directly drains into the IVC. The vena caval openings are considered as large openings with the diameter of 1.5-2 cm and medium when the diameter is 0.5-1.0 cm[11,12]. The distance of accessory vein from the main hepatic vein is important as it may be difficult to apply a single clamp if distance between accessory vein and the confluence of the hepatic vein 5 cm in the coronal plane.

DISCUSSION

EUS of hepatic vein and the tributaries is an operator dependent technique and in expert hands may give a mapping comparable to CT and magnetic resonance imaging. EUS of hepatic veins can help in identification of individual sectors and segments of liver. EUS offers additional superiority in assessing the flow dynamics of individual hepatic veins and can provide an opportunity for assessment of the anatomical features of hepatic vein length, diameter, pattern of joining, and evaluation of segmental venous drainage. Knowledge of the presence of supernumerary right hepatic veins or an inferior hepatic vein may facilitate extrahepatic or intrahepatic venous ligation during resection of the right hemi liver[13-16]. Studies done in animal models have shown a possible route for EUS guided intrahepatic portosystemic shunt from IVC and hepatic vein to portal vein[17]. The EUS anatomy of portal venous system has been well defined[18-20]. The assessment of hepatic veins can be also

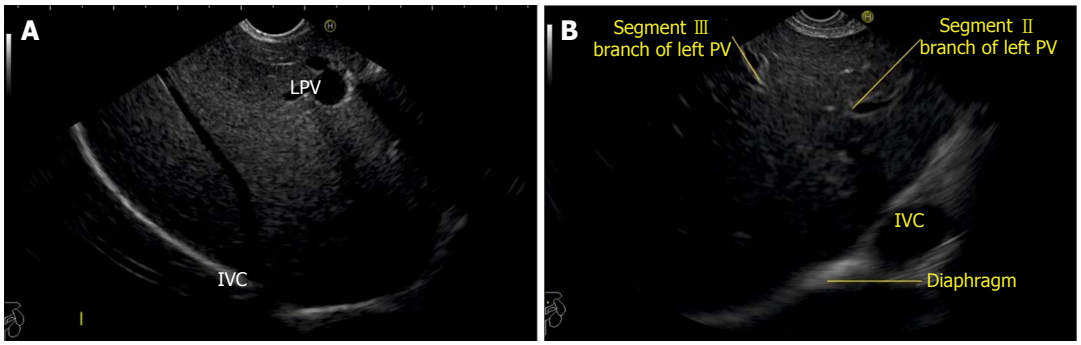

Figure 26 Endoscopic ultrasound from descending duodenum. A: Figure showing right hepatic vein; B: On anticlockwise rotation from 2nd part of duodenum, the inferior vena cava gradually moves from 9 o'clock position towards 4 o'clock position. LPV: Left portal vein; PV: Portal vein; IVC: Inferior vena cava.

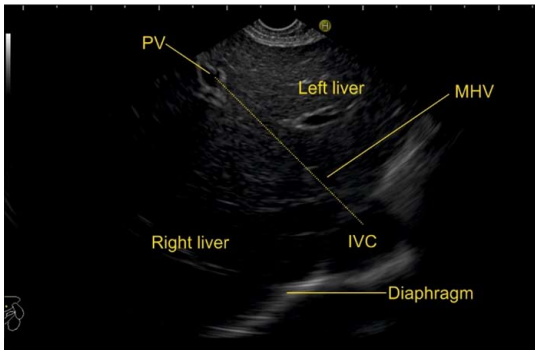

Figure 27 This figure shows the course of middle hepatic vein proceeding towards the portal vein by the dotted line and dividing the right anterior sector from the left medial sector. MHV: Middle hepatic vein; PV: Portal vein; IVC: Inferior vena cava.

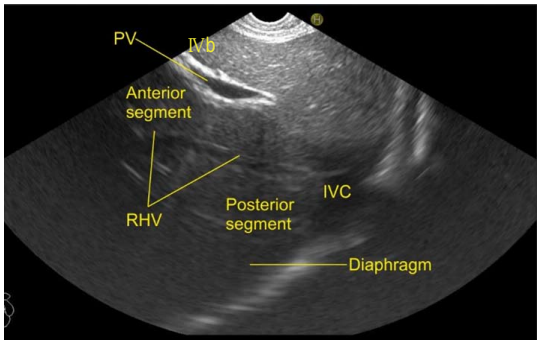

Figure 28 This figure shows the course of right hepatic vein dividing the anterior and posterior sector of right lobe of liver. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

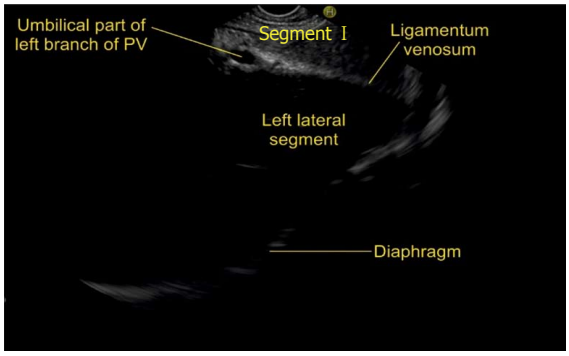

Figure 29 This figure shows the course of ligamentum venosum proceeding towards the umbilical part of portal vein and dividing the left lateral segment from the caudate lobe. The separation of left lateral and left medial segment is done by the course of left hepatic vein but more posteriorly near the liver hilum the ligamentum venosum separates left lateral segment from the caudate lobe. PV: Portal vein.

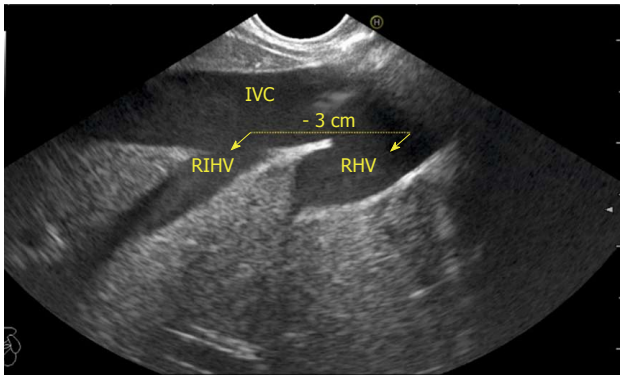

Figure 30 This image shows the presence of prominent right inferior hepatic vein below the right main hepatic vein. This vein has a size almost similar to main right hepatic vein and provides segmental drainage of a complete segment. The distance between right hepatic vein from the right inferior hepatic vein in this image is 3 cm. IVC: Inferior vena cava; RHV: Right hepatic vein; RIHV: Right inferior hepatic vein.

useful for assessing the path and possible techniques of specific hepatic vein puncture in planning a EUS guided procedures involving hepatic veins and portal vein (Figure 33).

CONCLUSION

This article describes a standard technique for visualization of hepatic veins. With practice an imaging of all the hepatic veins is possible from four stations. The imaging from fundus of stomach is the easiest and most convenient method of imaging of hepatic veins. EUS guided interventions may require approach from different stations. Knowledge of the hepatic venous territories and "venous drainage map" may provide

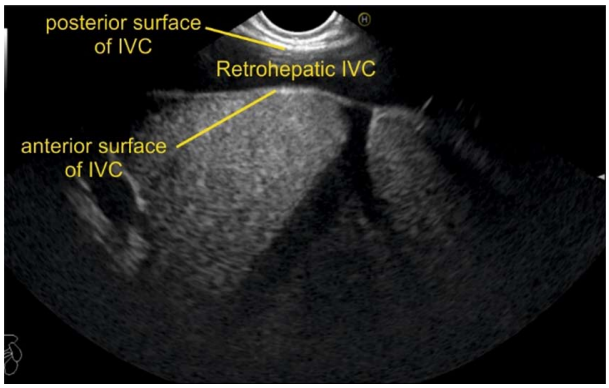

Figure 31 This image shows the right inferior accessory hepatic vein draining the right posterior sector. The presence of liver parenchyma above the joining of the vein points to retro rather than suprahepatic course of the vein. In this case the main right hepatic vein was absent and all the venous drainage was provided by the accessory vein. IVC: Inferior vena cava.

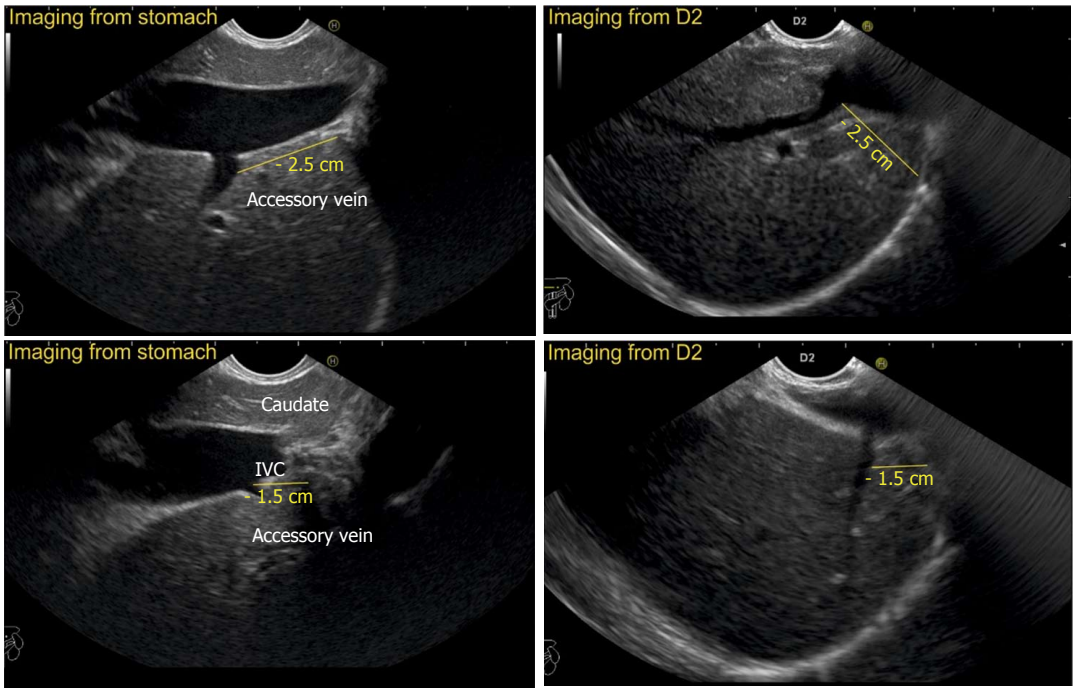

Figure 32 In this case, two accessory veins are seen about 1.5 cm and 2.5 cm below the diaphragm. A comparative imaging of the same accessory vein is shown from stomach and second part of duodenum.

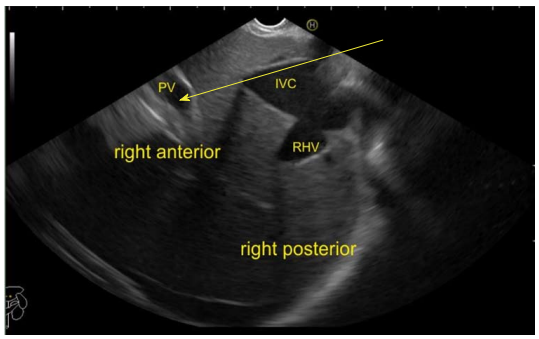

Figure 33 The imaging is done from abdominal part of esophagus and the main portal vein is seen on the far side of the screen. A possible communication is shown between the inferior vena cava and the main portal vein by the arrow. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

useful information for complex liver surgeries and therapeutic procedure involving hepatic veins.

ACKNOWLEDGMENTS

Pran Prakash (Graphic designer) for his contribution.

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P- Reviewer: Goral V, Hosoe N, Skok P **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 294-300

DOI: 10.4253/wjge.v10.i10.294

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Case Control Study

Economical effect of lumen apposing metal stents for treating benign foregut strictures

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Author contributions: Hallac A and Srikureja W designed research; Liu E, Dhumal P, Thatte A and Puri N performed research and contributed new reagents/analytic tools; all authors analyzed data and wrote the paper.

Institutional review board statement: Providence Health Care (Spokane) approves this study, and is part of the corresponding author home institution.

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

STROBE statement: The STROBE Statement has been adopted.

Manuscript source: Unsolicited Manuscript

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Received: June 29, 2018
Peer-review started: June 30, 2018
First decision: July 19, 2018
Revised: July 27, 2018
Accepted: August 21, 2018
Article in press: August 21, 2018
Published online: October 16, 2018

Abstract

AIM

To evaluate the clinical and economical efficacy of lumen apposing metal stent (LAMS) in the treatment of benign foregut strictures.

METHODS

A single center retrospective database of patients who underwent endoscopic treatment of benign foregut strictures between January 2014 and May 2017 was analyzed. A control group of non-stented patients who underwent three endoscopic dilations was compared to patients who underwent LAMS placement. Statistical tests performed included independent *t*-tests and five-parameter regression analysis

RESULTS

Nine hundred and ninety-eight foregut endoscopic dilations were performed between January 2014 and May 2017. 15 patients underwent endoscopic LAMS placement for treatment of benign foregut stricture. Thirty-six patients with recurrent benign foregut strictures underwent three or more endoscopic dilations without stent placement. The cost ratio of endoscopic dilation to LAMS (stent, placement and retrieval) is 5.77. Cost effective analysis demonstrated LAMS to be economical after three endoscopic dilation overall.

LAMS was cost effective after two dilations in the Post-surgical stricture subgroup.

CONCLUSION

Endoscopists should consider LAMS for the treatment of benign foregut strictures if symptoms persist past three endoscopic dilations. Post-surgical strictures may benefit from LAMS if symptoms persist after two dilations in a post-surgical. Early intervention with LAMS appears to be a clinically and economically viable option for durable symptomatic relief in patients with these strictures.

Key words: Benign esophageal stricture; Endoscopy economics; Stent economics; Self expandable metallic stents; Esophageal diseases

Core tip: The findings of our study will be helpful with clinical decision making when treating benign strictures of the esophagus and foregut. The main finding of our study is that lumen apposing metal stents have the potential to have an economical advantage over repeated dilations in the treatment of recurrent benign foregut strictures. Reports of placing lumen apposing stents as an alternative to serial endoscopic dilation have been reported, however no economic analysis has been published.

Hallac A, Srikureja W, Liu E, Dhumal P, Thatte A, Puri N. Economical effect of lumen apposing metal stents for treating benign foregut strictures. *World J Gastrointest Endosc* 2018; 10(10): 294-300 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/294.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.294

INTRODUCTION

Pathological or therapeutic disruption of the foregut tissue is common, yet diverse in both its etiology and severity. Surgical anastomosis, peptic injury, radiation, caustic ingestion, eosinophilic esophagitis, Schatzki rings and esophageal webs all disrupt the innate tissue and predispose to luminal stricture formation[1,2]. The mechanism by which esophageal strictures develop is hypothesized to be the result of fibrous tissue production and collagen deposition stimulated by deep ulceration or chronic inflammation[3,4]. The principle symptoms of foregut stricture disease include, dysphagia, early satiety, epigastric pain, heart burn, nausea and vomiting. The current gold standard treatment of foregut strictures is endoscopic dilation. It is not uncommon for patients to undergo multiple dilations to achieve remission, while some have persistent disease forcing clinicians to face challenging management decisions. Currently, there are no established reliable predictors to identify which strictures will respond optimally to dilation. Additionally, there is no expert consensus regarding the frequency of dilations necessary to define a refractory structure[5].

An evolving, but "off label" treatment for benign foregut strictures is placing stents for sustained esophageal patency. The use of self-expandable metal stents (SEMS) has the benefit of providing an ongoing radial force to suppress the stricture and maintain luminal patency. The SEMS design has been innovated upon, ultimately resulting in the creation of the lumen apposing metal stent (LAMS). LAMS are short, self-expanding, fully covered, metal stents with large flanges that anchor the stent at both ends.

Clinical guidelines, supported by large studies and systemic reviews have validated the use of stents as an acceptable salvage therapy in the treatment of refractory benign and malignant strictures; however, these studies did not include LAMS[5-10].

The objective of this study is to examine the use of LAMS in the treatment of benign foregut strictures. Case series and case reports have documented the use of LAMS in benign strictures of various etiology at different locations in the foregut[11-17]. We aim to illustrate the clinical effectiveness and economics of LAMS.

MATERIALS AND METHODS

Institutional review board approval was obtained for the development of a retrospective database to evaluate the efficacy of LAMS in the treatment of benign foregut strictures. The database used for this study included all patients who underwent endoscopic dilation or LAMS placement for treatment of benign foregut strictures at a single non-university tertiary care center. The database was constructed by manual review of the electronic health record (EHR) system of a large regional health system. This retrospective case-control study was reported in accordance with the STROBE statement[18].

Current procedural terminology (CPT) codes were used to identify the most recent 1000 controlled radial balloon dilation (CRE) and Savary-Gilliard dilations of the foregut. All endoscopic procedures performed between January 2014 and May 2017 was reviewed, 998 procedures were identified. These procedures were reviewed to isolate all patients who underwent three or more CRE or Savary-Gilliard dilations during the 40-mo period, and 36 patients fit these criteria. Three or more dilations were selected as our inclusion criteria for recurrent strictures based on the fact that LAMS placement required a minimum of two endoscopies and LAMS placement is rarely first line therapy at our institution. The 36 patients' medical records were interrogated to establish a control group for the comparison of LAMS versus serial endoscopic dilation.

Fifteen patients underwent endoscopic LAMS placement for treatment of benign foregut stricture disease. The LAMS were placed without electrocautery or sutures with the intention of maintaining luminal patency for 90 d or until surgical revision. The LAMS utilized were 10 mm in length, fully covered, with bilateral 21 mm or 24

Table 1 The mean time between dilations for all patients in the recurrent dilation group

	n	Mean time between dilations (d)	SD	*t*	*P*
Male	20	146.8	169.7	-0.01	0.9
Female	16	147.5	141.1		
Non-Surgical	31	137.6	159.9	-1.1	0.3
Surgical	5	205.7	121.4		

mm flanges. When deployed the stent self-expanded to a luminal diameter of 10 mm or 15 mm (Axios™ Stent, Boston Scientific©, Marlborough, MA, United States). The patients who underwent LAMS placement consented to undergoing treatment with a medical device in an "off label" non-United States Federal Drug Enforcement Agency (FDA) approved indication.

Clinical end points were the number of symptom free days and the number of days between endoscopic dilations. The number of symptom free days and days between each endoscopic procedure was determined by documentation in the EHR and reported as mean time between dilations (MTBD) and mean symptom free days (MSFD). The review of EHR documentations was performed by a physician who is not a gastroenterologist to prevent potential bias. Complications were defined as removal of the stent prior to the intended 90-d duration of placement or hospital admission for gastrointestinal symptoms. Endoscopies performed prior to this study's 2014 start date were reviewed when available.

Statistical analysis

All statistical analysis was performed by a biostastician using IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY, United States). Statistical tests performed included independent *t*-tests and five-parameter regression analysis with the independent variable being endoscopic dilations as pair indices and the dependent variable being time. All patients that lacked sufficient follow up to accurately characterize their post stent clinical course were included in the descriptive statistical analysis and excluded from the case control analysis. Statistical significance was determined using a threshold of $P = 0.05$.

Economic analysis

The economic analysis was designed utilizing the recommendations of the International Association of Health Technology Agencies to increase generalizability to clinical gastroenterologists[19]. The 2016 Medicare National Average Payment fee schedule that was issued by Center for Medicare and Medicaid Services in January of 2016 was used to determine the cost of endoscopic interventions. A 2% reduction was calculated on all costs to reflect the sequestrations placed by the United States government on all Medicare rates. The cost we associated with each endoscopic dilation is the mean cost of a CRE and Savary-Gilliard dilations. The cost of the LAMS was the specific per unit cost at our institution. The breakeven number for using a stent is calculated by dividing the delta between the MSFD and MTBD by the coefficient of the regression.

RESULTS

Recurrent dilation group

Strictures of non-anastomotic origin accounted for 86.1% ($n = 31$). Five post-surgical strictures located at anastomotic sites accounted for 13.9% of the recurrent dilation group (Table 1). Patients' ages ranged from 26 to 90 years with a median of 66 years of age. The majority of patients were men (55.6%, $n = 20$). The MTBD was 147 ± 156 d.

The regression results demonstrate that after the initial endoscopic dilation, patients with recurrent benign esophageal strictures will have a decreased time between subsequent dilations that averages 28 d. The reduction of time between subsequent dilations was 20 d in non-surgical strictures and 64 d in postoperative strictures.

LAMS group

The LAMS group consisted of 15 patients who underwent endoscopic LAMS placement as an adjunctive treatment for various benign strictures of the foregut (Table 2). Strictures occurred post surgically at locations including: Gastrojejunal anastomosis (GJ), Roux-en-Y gastric bypass (RYGB), vertical band gastroplasty (VBG), esophagogastric anastomosis (EG). The majority of the LAMS group were post-surgical strictures, of which 27% ($n = 4$) resulted from weight loss surgeries. Thirteen percent ($n = 2$) of patients had post procedural dysphagia and abdominal pain leading to elective premature LAMS removal (Table 2). Patient eight obtained partial relief of dysphagia on the initial LAMS which recurred promptly after LAMS removal prompting insertion of a second LAMS 21 d later intended to provide symptomatic relief prior to surgical intervention. Patient 14 underwent LAMS placement for a persistent peptic stricture of the duodenal bulb which initially relieved some symptoms, however; symptoms recurred and the LAMS was removed and replaced 74 d later for worsening symptoms.

The median length of follow up was 299 d (range, 7-628). The median duration of the endoscopic LAMS placement was 14.7 min (range, 3.3-68.3), LAMS removal had a median endoscopy duration of 14.7 min (range, 1.7-28.2).

Sixty percent ($n = 8$) of the LAMS group had sufficient follow up for inclusion in a multivariate regression

Table 2 Pre and post lumen apposing metal stent details for the all patients who underwent endoscopic treatment during a 40-mo period at a non-university tertiary care center

Patient	Age (yr)	Gender	Anastomotic Stricture (Yes/No)	Stricture location	Prior foregut surgery	EGD dilations prior to stenting	Duration of stent insertion (d)	Stent migration (Yes/No)	Adverse Events	Symptomatic relief	Post stent Interventions
1	59	M	Yes	GJ	RYGB	2	168	No	No	Yes	No
2	46	F	Yes	GJ	RYGB	3	91	No	No	Yes	No
3[1]	62	F	Yes	GJ	Distal gastrectomy	3	90	No	No	Yes	Surgical Revision
4[1]	86	M	No	Pyloric channel	Subtotal gastrectomy	3	138	No	No	Yes	No
5[1]	90	M	No	Distal esophagus	Nissen fundoplication	3	91	No	No	Yes	No
6	78	F	No	Distal esophagus	Nissen fundoplication	4	31	No	No	Yes	No
7	65	F	No	Pyloric channel	No	2	< 159	Yes	No	Yes	No
8[1]	65	F	No	Mid Gastric Body	VBG	1	Stent 1: 184, Stent 2: 162	No	No	Yes	Surgical VBG removal
9	73	F	No	Pyloric channel	No	2	98	No	No	Yes	No
10	78	F	No	Mid Gastric Body	VBG	3	-	-	No	Yes	-
11	72	M	Yes	EG	ILE	0	50	No	No	Yes	No
12[1]	56	M	Yes	EG	ILE	4	15	No	Yes-Chest pain	No	Yes-EGD dilation
13[1]	73	F	Yes	EG	Total gastrectomy	3	7	No	Yes-Abdominal Pain	No	Yes-EGD dilation
14	69	M	No	First duodenal segment	No	1	Stent 1: 116 Stent 2: 265	No	No	No	-
15	78	M	No	Duodenal bulb	No	3	20	No	Yes- Obstructive jaundice from stent pressure	No	-

[1]Indicates patients included in the multivariate regression analysis. M: Male; F: Female; GJ: Gastro-jejunal anastomosis; RYGB: Roux-en-Y gastric bypass; VBG: Vertical band gastroplasty; EG: Esophago-gastric anastomosis; D1: Duodenal segment 1; D2: Duodenal segment 2.

analysis (Table 3). Of the eight patients in the LAMS group included in the multivariate analysis, 63% (n = 5) had benign esophageal strictures, and 25% (n = 2) had pyloric stenosis. No difference was seen when performing an independent t test comparing patient gender and MSFD (t = - 0.014, P = 0.95) in patients treated with LAMS. Similarly, surgical versus non-surgical stricture etiology did not demonstrate a difference in MSFD (t = 0.72, P = 0.511).

Clinical comparison

Comparing the MTBD of the 36 patients in the dilation group with that of the LAMS group showed a higher number of symptom free days in each analyzed subcategory (Table 4). Significant differences in the MTBD are demonstrated when comparing all patients in the LAMS group versus their recurrent dilation counterpart (P = 0.011). Sub-analysis dividing the patients by gender and surgical setting (if the stricture was post-surgical) showed that males who underwent LAMS placement reported significantly more symptom free days than their recurrent dilation group counterpart (P = 0.013) (Table 4).

Table 3 Regression analysis of the time between dilation (d) for patients who underwent lumen apposing metal stent placement

	R^2	Intercept	Coefficient	*F*	*P*
Mean overall	68.3%	220.3	-27.8	8.6	0.04
Mean female	16.9%	192	-17.4	0.8	0.41
Mean male	96.1%	250	-39.3	99.3	0.001
Mean surgical	62.2%	96.2	-63.3	6.5	0.06
Mean nonsurgical	62.8%	188.3	-19.4	6.7	0.06

Table 4 The comparison of clinical outcomes in the lumen apposing metal stent and recurrent dilation groups

	Group	*n*	Mean symptom free days	SD	*t*	*P* (two tail)
Overall	Dilation	36	153	153.7	2.9	0.01
	LAMS	8	327	156.9		
Male	Dilation	20	147	169.04	3.5	0.01
	LAMS	3	347	73.7		
Female	Dilation	16	160	137.2	2.1	0.09
	LAMS	5	353	190.9		
Nonsurgical	Dilation	31	144	158.7	1.5	0.26
	LAMS	3	298	165.6		
Surgical	Dilation	5	209	114.08	2.06	0.07
	LAMS	5	382	148.8		

LAMS: Lumen apposing metal stent.

Table 5 The economic analysis for lumen apposing metal stent utilization

	MSFD	MSFD/Cost Ratio	MTBD	Coefficient from Regression	Breakeven *n*
Overall	327	56.7	153	27.8	3.4
Male	347	60.1	147	39.3	2.2
Surgical	382	66.2	209	63.3	2.2

MSFD: Mean symptom free days; MTBD: Mean time between dilations (d).

Economic analysis results

The average cost of an endoscopic dilation is $1282, whereas the cost of a LAMS is $4060, endoscopic insertion and endoscopic removal cost $2399 and $937 respectively. The total cost for the LAMS and endoscopic insertion and removal is $7396; thus, a cost ratio is 5.7. Dividing the overall MSFD for the LAMS group and the recurrent dilation group by the cost ratio demonstrates that LAMS placement only became economical when the time between dilation is less than or equal to 57 d (Table 5). The overall MTBD for the recurrent dilation and LAMS group is 152 d. The overall breakeven number for using LAMS is 3.5 dilations, thus endoscopic LAMS placement is economical after the three dilations.

DISCUSSION

The use of esophageal prosthesis began over a century ago and progressed into commercially available applications in the 1970s. The current generation of SEMS were initially used in the biliary tree before being developed into esophageal specific applications in the 1990's[20]. The recommended use of SEMS is most clearly defined in the malignant stricture population; however, ambiguity exists in the use of SEMS in benign strictures of the gastrointestinal tract. Complications of stent migration and variability in efficacy of SEMS have limited their use in benign strictures.

The FDA approved the first LAMS in 2012 for the endoscopic treatment of pancreatic pseudocysts[21]. There is a paucity of published experience using LAMS in the treatment of benign foregut strictures, with only three studies, including ours, containing 15 or more patients[11,12]. The limited number of studies utilizing LAMS in benign stricture disease is primarily due to the low use of "off label" non-FDA approved devices. As such, we believe our results along with Irani *et al*[12] and Yang *et al*[11]'s showcase the utility of LAMS in the treatment of benign foregut strictures.

Clinical outcomes

Our results are most similar to the prospective multicenter trial performed by Yang *et al*[11]. Yang *et al*[11]'s cohort included 23 patients who underwent an average of 3.7 endoscopic dilations prior to LAMS placement. As such, this demonstrated the generalizability of our control group, which included individuals who underwent three or more endoscopic dilations. In addition to the 23 foregut LAMS placements, Yang *et al*[11]'s cohort included four colonic stricture stent placements with 60 d (IQR, 40-90 d) median duration of LAMS placement compared to our median of 96 d (IQR, 41-161 d). Both our cohort

and Yang *et al*[11]'s did not experience any tissue overgrowth or technical difficulties with LAMS removal; yet, these issues were encountered in Irani *et al*[12]'s series. The adverse events related to LAMS extraction could be more prevalent in Irani *et al*[12]'s series due to their 300 d median follow up time post LAMS insertion, which is slightly larger than both Yang *et al*[11]'s and our own cohort, which had median follow up times of 100 and 299 d respectively. Yang *et al*[11], Irani *et al*[12] and our own cohort all reported encountering patients with pain following LAMS insertion that was severe enough to prompt premature LAMS removal, the mean incidence of premature LAMS removal due to pain was 6% (range, 4.3%-7%). Our study included a unique adverse event after LAMS was placed across a duodenal bulb stricture (Table 2, Patient 15), in which the distal flange of the stent created backpressure on the intraduodenal segment of the common bile duct leading to abdominal pain and obstructive jaundice resulting in stent removal 20 d after placement.

Stent migration

In 2015, Fuccio *et al*[9] performed a meta-analysis of SEMS use in refractory benign esophageal stricture. Fuccio *et al*[9]'s meta-analysis reported a stent migration rate of 36% in fully covered self-expanding metal stents (FCSEMS)[9]. Twenty-two percent of the patients in Fuccio *et al*[9]'s analysis who underwent FCSEMS placement met the Kochman *et al*[22]'s criteria for refractory benign esophageal stricture meaning they underwent at least five dilation sessions and/or cycles with dilation to at least 14 mm.

LAMS migration was confirmed in one of 15 patients in this study although a second stent migration could have occurred in the single patient lost to follow up (Table 2, Patient 11). Our reported LAMS migration rate of 6.7%-13.3% of patients is consistent with the two largest studies of LAMS that collectively had a migration rate of 7.5% in their 58 cases[12,13].

Clinical success

Eighty-one percent of patients in our study had symptomatic relief. Repeat endoscopic procedures after LAMS placement was limited to stent exchanges in two patients and a non-therapeutic endoscopy in one patient. LAMS successfully controlled symptoms in two patients prior to undergoing revision gastric surgery. Approximately 83% of patients were symptom free at 100 d after LAMS removal in Yang *et al*[11]'s study, and the clinical success rate at 6 mo follow up was 61% in Irani *et al*[12]'s study.

Economic analysis

The cost breakeven point of the overall group is 3.5 and 2.2 dilations in the post-surgical group, which shows that stent placement may have an economical advantage over recurrent dilation after the third dilation. The male subgroup demonstrated a cost breakeven point after the second dilation; however, this finding is limited by a lack of sufficient number of subjects to provide a female subgroup analysis. Although our study did not utilize Kochman *et al*[22]'s criteria for refractory benign esophageal strictures as an inclusion requirement, applying our breakeven point for LAMS placement would demonstrate LAMS to be cost effective in all benign recurrent esophageal strictures as defined by Kochman *et al*[22].

Endoscopists should welcome LAMS as a second line therapy for benign foregut strictures, as it has shown to be a clinically and economically effective treatment modality for managing the devastating symptoms of benign foregut strictures.

An interesting secondary finding from the analysis of the control group was the time between dilations was decreasing by 28 d between each dilation. This surprising finding should be expanded on in further studies that aim to elucidate the pathogenesis of benign foregut stricture formation.

The most significant limitation of our study beyond those inherent to retrospective analysis is the low sample size; however, this is to be expected in the study of a non-FDA approved use of a medical device. The absence of a formal symptom scoring system at post procedure clinic visits and the inability to follow all subjects long term makes our data mildly vulnerable to subject reporting and selection bias. More prospective trials are needed to develop a professional consensus on the role of LAMS in the treatment of benign foregut strictures.

ARTICLE HIGHLIGHTS

Research background

The use of lumen apposing metal stents (LAMS) began in 2012 as a treatment modality for pancreatic pseudocysts. Currently, LAMS are being used in various endoscopic procedures such as pancreatic pseudocyst drainage.

Research motivation

The key question of our study is How effective and economical is the use of LAMS in the treatment of benign foregut strictures.

Research objectives

The main objective of this study was to determine how to appropriately utilize LAMS in the treatment of benign foregut strictures. Benign foregut strictures frequently recur therefore this study will contribute to the literature used to determine treatment strategies for these difficult recurrent strictures.

Research methods

The research methods that were adopted to realize our objective was a single center retrospective case-control study. The case-control study was complemented by a cost effectiveness analysis.

Research results

The cost breakeven point of using a LAMS compared to repeat endoscopic dilation was 3.5 and 2.2 dilations in patients with benign foregut strictures and post-surgical strictures, respectively. Our results demonstrate that stent placement may have an economical advantage over recurrent dilation once a patient has undergone three endoscopic dilations. The optimal duration of stent placement to provide maximum efficacy and minimum adverse events remains unknown, further prospective multicenter studies are needed.

Research conclusions

This study presents the novel finding that inserting a LAMS instead of serial

dilations can be a cost-effective treatment. We believe our results demonstrate that recurrent endoscopic dilation of benign foregut strictures can be optimally treated by LAMS in well selected patients. In summary, this study demonstrates that the interval between endoscopic dilations decreases overtime after each subsequent dilation. The use of LAMS for benign foregut strictures has been reported however we utilized an economic analysis to prove our hypothesis that there is a potential cost savings.

Research perspectives

This study has important clinical implications particularly in the United States where the placement of a LAMS for any reason other than evacuating a pancreatic pseudocyst is not Federal Drug Enforcement Agency approved. Endoscopists can incorporate the findings of this study into their clinical practice when treating patients whose benign foregut strictures continue to require endoscopic dilations.

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P- Reviewer: Bilir C, Chow WK, Fiori E, Fogli L, Giannopoulos G, Goral V**,** Lee CL, Zhu YL **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 301-307

DOI: 10.4253/wjge.v10.i10.301

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Yield of capsule endoscopy in obscure gastrointestinal bleeding: A comparative study between premenopausal and menopausal women

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Author contributions: Silva JC and Pinho R designed the study, performed the research, analyzed the data and wrote the paper; Rodrigues A, Ponte A, Rodrigues JP, Sousa M, Gomes C and Carvalho J performed the research and analyzed the data.

Institutional review board statement: The study was reviewed and approved by the review board of Centro Hospital de Vila Nova de Gaia/Espinho.

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

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

Manuscript source: Invited manuscript

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Received: April 30, 2018
Peer-review started: April 30, 2018
First decision: June 6, 2018
Revised: July 6, 2018
Accepted: August 1, 2018
Article in press: August 1, 2018
Published online: October 16, 2018

Abstract

AIM

To evaluate differences in capsule endoscopy (CE) performed in the setting of obscure gastrointestinal bleeding (OGIB) among premenopausal women (PMW) and menopausal women (MW).

METHODS

Retrospective, single-center study, including female patients submitted to CE in the setting of OGIB between May 2011 and December 2016. Patients were divided into 2 groups according to age, considering fertile age as $\leqslant$ 55 years and postmenopausal age as > 55 years. The diagnostic yield (DY), the rebleeding rate and the time to rebleed were evaluated and compared between groups. Rebleeding was defined as a drop of Hb > 2 g/dL or need for transfusional support or presence of melena/hematochezia.

RESULTS

A hundred and eighty three female patients underwent CE for OGIB, of whom 30.6% (n = 56) were PMW and 69.4% (n = 127) were MW. The DY was 30.4% in PMW and 63.8% in MW. The most common findings were angiodysplasias in both groups (PMW: 21.4%, MW: 44.9%) (P = 0.003). In PMW, only 1.8% required therapeutic endoscopy. In 17.3% of MW, CE findings

led to additional endoscopic treatment. Rebleeding at 1, 3 and 5 years in PMW was 3.6%, 10.2%, 10.2% and 22.0%, 32.3% and 34.2% in MW. Postmenopausal status was significantly associated with higher DY (P < 0.001), TY (P = 0.003), rebleeding (P = 0.031) and lower time to rebleed (P = 0.001).

CONCLUSION

PMW with suspected OGIB are less likely to have significant findings in CE. In MW DY, need for endoscopic treatment and rebleeding were significantly higher while time to rebleed was lower.

Key words: Diagnostic yield; Obscure gastrointestinal bleeding; Premenopausal women; Menopausal women; Capsule endoscopy

Core tip: Patients with negative findings in oesophagogastroduodenoscopy and colonoscopy with suspected obscure gastrointestinal-bleeding benefit from further capsule endoscopy (CE) study. Premenopausal women are frequently referred for CE. However in this subset of patients the pretest probability of positive findings is thought to be low. This paper compared the diagnostic yield (DY) as well as therapeutic yield (TY), rebleeding, hospitalization and mortality between premenopausal and menopausal women. We found that menopause status was significantly associated with positive findings, DY, TY, rebleeding and lower time to rebleed. This may lead to consider the exclusion of other comorbid pathologies in fertile age women before CE.

Silva JC, Pinho R, Rodrigues A, Ponte A, Rodrigues JP, Sousa M, Gomes C, Carvalho J. Yield of capsule endoscopy in obscure gastrointestinal bleeding: A comparative study between premenopausal and menopausal women. *World J Gastrointest Endosc* 2018; 10(10): 301-307 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/301.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.301

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) accounts for approximately 5% of all cases of gastrointestinal (GI) bleeding and is usually due to a lesion in the small bowel[1]. OGIB can be classified as overt or occult[2]. In patients who have documented overt GI bleeding (excluding hematemesis) and negative findings on high-quality oesophagogastroduodenoscopy (OGD) and colonoscopy, capsule endoscopy (CE) is recommended as the next diagnostic step[3]. Patients with occult GI blood loss and negative findings in OGD and colonoscopy need comprehensive evaluation, including CE to identify an intestinal bleeding lesion[4]. In premenopausal women (PMW) gynecologic etiologies are the most frequent cause of anemia, although GI bleeding is reported as a cause of anemia in 12%-30%[5,6]. Re-bleeding after negative CE study in PMW is often due to menstrual blood loss[7-9]. Taking this in consideration it is necessary to clarify the differences in DY, TY and rebleeding in OGIB between PMW and MW. In PMW with suspected OGIB CE study may not be the first choice, considering the possibility of gynecologic blood loss and the lower rates of small bowel lesions[10].

Diagnostic yield (DY) of CE has already been evaluated, particularly in OGIB[11-13]. Age is an important factor, and more frequently older patients are referred for OGIB investigation through CE. In this group of patients DY is higher[14].

Few trials have compared CE findings in OGIB according to the menopausal status and some reported a lower DY in CE performed in PMW[10,15].

The present study aimed to evaluate and compare the DY of CE between PMW and menopausal women (MW). Secondary outcomes included a comparison of therapeutic yield (TY), rebleeding, hospitalization and mortality for OGIB between PMW and MW who underwent CE.

MATERIALS AND METHODS

Patient and data collection

A cohort of female patients with OGIB who underwent CE after bidirectional endoscopy at Centro Hospital Vila Nova de Gaia from May 2011 to December 2016 was evaluated. Patients were followed-up until April 2018. Patients were then divided into 2 groups according to age, considering fertile age as ⩽ 55 years and postmenopausal age as > 55 years.

Patient clinical information was retrospectively collected from electronic medical records, and included demographic characteristics (gender, age); comorbidities (cardiovascular, renal, hepatic disease); medical therapy [anticoagulants, antiplatelet and nonsteroidal anti-inflammatory drugs (NSAIDs)]; hemoglobin (Hg) at admission and number of units of packed red blood cells (RBC) transfused prior to CE.

CE

Written informed consent was obtained from all patients. In this study the Mirocam® Video Capsule system was used and the examinations were carried out according to our unit protocol. Patients underwent a clear liquid diet the day before and a fasting period of 12 h before the exam. Oral iron supplements were suspended at least 8 d before the procedure.

After CE ingestion, patients were evaluated 1-2 h after, through realtime visualization and a prokinetic agent was administered if the CE was retained in the stomach. Oral light diet was initiated 4 h after CE ingestion. The recorder was removed 12 h after CE ingestion. Earlier removal of the recorder demanded realtime visualization, confirming a colonic location of

Table 1 Patient characteristics *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Age (mean ± SD, yr)	64.3 ± 15.8	43.7 ± 8.0	74.3 ± 7.9	< 0.001
Comorbidities				
Chronic kidney disease	24 (13.1)	0 (0)	24 (18.9)	< 0.001
Coronary artery disease	20 (10.9)	3 (5.4)	17 (13.4)	0.11
Heart failure	47 (25.7)	0 (0)	47 (37.0)	< 0.001
Hepatic disease	7 (3.8)	1 (1.8)	6 (4.7)	0.34
Atrial fibrillation	33 (18.0)	2 (3.6)	31 (34.4)	0.001
Drugs				
Anticoagulation	35 (19.1)	2 (3.6)	33 (26.0)	< 0.001
Anti-platelet drugs	57 (31.1)	6 (10.7)	51 (40.2)	< 0.001
NSAIDs	61 (33.3)	8 (14.3)	53 (41.7)	< 0.001

[1]*t* -test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance; PMW: Premenopausal women; MW: Menopausal women; NSAIDs: Nonsteroidal anti-inflammatory drug.

CE.

CE cleansing was evaluated according to the qualitative scale developed by Brotz *et al*[16], and appropriate cleansing was assumed when graduated as excellent, good or fair.

CE findings were classified as positive and negative findings. Positive findings included bleeding without visible lesions, angiodysplasia, varices, hemangioma, ulcer, erosion, eroded polyps, diverticulum with bleeding stigmata or small-bowel tumor.

The DY was defined as the proportion of CE with positive findings compared to the total number of female patients included in the study. The TY was defined as the proportion of patients performing endoscopic treatment compared to the total number of female patients included in the study. Rebleeding, time to rebleed, hospitalization and mortality were also evaluated. Rebleeding episodes were defined as evidence of melena or hematochezia, a drop in Hg ⩾ 2 g/dL from baseline, and/or the need for transfusion[17-19].

Statistical analysis

Data were analyzed using SPSS version 23.0. Descriptive statistics were used to describe the patient's demographic features, clinical characteristics and type of endoscopic findings. Categorical variables were presented as percentages and numeric variables as means. Results are expressed as percentages or mean ± SD for continuous variables.

The χ^2 test was used to compare non-continuous variables. The *t*-test was used to compare continuous variables. The Kaplan-Meier test was used to calculate the time to rebleed. The Log-Rank test was used to compare the time to rebleed between groups. A $P < 0.05$ was considered to be statistically significant.

RESULTS

Sample analysis

In our study, 183 female patients underwent CE for OGIB, of whom 30.6% were PMW (*n* = 56) and 69.4% were MW (*n* = 127). Patient characteristics are shown in Table 1. The mean age was 64.3 years (SD 15.8). Most patients were referred for occult OGIB (82.5%, *n* = 151), while 17.5% (*n* = 32) had overt OGIB. Iron deficiency anemia (IDA) was the most common indication (81.4%, *n* = 149) followed by melena (9.8%, *n* = 18), hematochezia (7.7%, *n* = 14) and positive fecal occult blood test (1.1%, *n* = 2). Mean Hg value before CE was 9.7 g/dL (SD 2.0). OGIB needing transfusional support was identified in 34.4% (*n* = 63). Indication for CE, mean Hg value and need of transfusional support are shown in Table 2.

Concerning comorbidities, 25.7% had heart failure (*n* = 47), 18% had atrial fibrillation (*n* = 33), 13.1% had chronic kidney disease (*n* = 24) and 3.8% had liver disease (*n* = 7). Drugs increasing bleeding risk were also evaluated: 19.1% took vitamin K antagonists or direct oral anticoagulants, 31.2% were medicated with aspirin or thienopyridines and 33.3% took NSAIDs.

CE findings are presented in Table 3. Small bowel cleansing was considered appropriate in 77.6% (*n* = 142) CE studies. Most patients had positive findings (66.7%, *n* = 122). Angiodysplasias were the most frequent finding (37.7%, *n* = 69) followed by ulcers/erosions (9.8%, *n* = 18) (Figure 1) and mass lesions (8.7%), namely tumors 7.1% [gastrointestinal stromal tumor (GIST) and subepitelial lesions] and polyps 1.6%. Blood in the GI tract was observed in 12.6% CE (*n* = 23), of which in 60.9% no lesions were identified. Angiodysplasias were classified according to the Saurin *et al*[7] classification system as P1 (66.7%, *n* = 46) and P2 (33.3%, *n* = 23). Considering the timing of CE most patients were studied > 14 d (88.0%, *n* = 161) while a minority underwent CE within the first 14 d (48 h-14 d in 8.2%, *n* = 15 and < 48 h in 3.8%, *n* = 7).

The outcomes of CE are shown in Table 4. The DY was 53.6% (*n* = 98), TY 12.6% (*n* = 23). The rebleeding rate was 16.4%, at 1 year, 25.8%, at 3 years and 27.2% at 5 years (Figure 2). The hospitalization rate was 7.1% (*n* = 13) and the global mortality 1.0% (*n* = 2) (Table 4).

Table 2 Indication, mean hemoglobin value and need of transfusional support in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Indication for CE				0.11
Occult OGIB	151 (82.5)	50 (89.3)	101 (79.5)	
Overt OGIB	32 (17.5)	6 (10.7)	26 (20.5)	
IDA	149 (81.4)	50 (89.3)	99 (78.0)	
Positive fecal occult blood test	2 (1.1)	0 (0)	2 (1.6)	
Hematochezia	14 (7.7)	2 (3.6)	12 (9.4)	
Melena	18 (9.8)	4 (7.1)	14 (11.0)	
Hb prior to CE, g/dL	9.7 (± 2.0)	10.4 (± 1.7)	9.3 (± 2.1)	0.001
Need of transfusional support prior to CE	63 (34.4)	7 (12.5)	56 (44.1)	< 0.001

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; PMW: Premenopausal women; MW: Menopausal women; OGIB: Obscure gastrointestinal bleeding; IDA: Iron deficiency anemia; Hb: Hemoglobin.

Table 3 Capsule Endoscopy findings in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Positive Findings	122 (66.7)	31 (55.4)	91 (71.7)	0.031
CE Findings				
Angiodysplasias	69 (37.7)	12 (21.4)	57 (44.9)	
Ulcers/erosions	18 (9.8)	11 (19.6)	7 (5.5)	
Mass lesions	16 (8.7)	5 (8.9)	11 (8.7)	
Meckel's diverticulum	3 (1.6)	0 (0)	3 (2.4)	
Other	2 (1.0)	2 (3.6)	0 (0)	
Saurin's Classification				0.043
P1	46 (66.7)	11 (91.7)	35 (61.4)	
P2	23 (33.3)	1 (8.3)	22 (38.6)	
Blood in GI tract	23 (12.6)	3 (5.4)	20 (15.7)	0.051
Blood with no lesions	14 (7.7)	1 (1.8)	13 (10.2)	
Adequate small bowel cleansing	142 (77.6)	44 (78.6)	56 (44.1)	0.83

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; PMW: Premenopausal women; MW: Menopausal women; Saurin *et al*[7] Classification: Positive-P2 (high potential for bleeding) and negative-P1 (uncertain hemorrhagic potential).

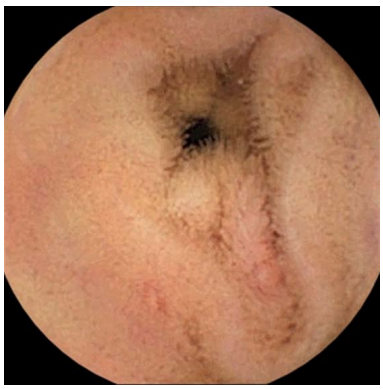

Figure 1 Capsule endoscopy of menopausal women with milimetric erosions in the jejunum.

Per group analysis

The mean age of MW was 73.4 ± 7.9 years and for PMW 43.7 ± 8.0 years. Post-menopausal age was associated with significantly higher comorbidities, namely heart failure (*P* < 0.001), chronic kidney disease (*P* < 0.001) and atrial fibrillation (*P* = 0.001). In this group use of anticoagulants, anti-aggregants and NSAIDs was significantly higher (*P* < 0.001). Mean Hg level at CE study was lower in MW (9.3 ± 2.1 g/dL) compared to PMW (10.4 ± 1.7 g/dL). The need of blood transfusion before CE was significantly higher in MW (44.1% *vs* 12.5%) (*P* < 0.001). IDA was the most common indication in both groups (MW 78.0%; PMW 89.3%).

MW had more frequently positive findings in CE study (71.1% *vs* 55.4%) (*P* = 0.031). Angiodysplasias were the most frequent finding in both groups, diagnosed in 44.9% of MW (*n* = 57) and in 21.4% of PMW (*n* = 12) (*P* = 0.003). MW had more frequently lesions with a high bleeding potential, classified as P2 lesions (38.6% *vs* 8.3%) (*P* = 0.043). Blood in the GI tract was identified more frequently in MW (15.7%, *n* = 20) than PMW (5.4%, *n* = 3) (*P* = 0.051). Cleansing adequacy was not significantly different between groups (*P* = 0.83). Timing to CE was not significantly different between groups (*P* = 0.31). However in MW timing of CE was associated with higher DY (*P* = 0.002) and TY (0.024). In PMW there timing to CE was not associated with higher DY (*P* = 0.23) nor TY (*P* = 0.96).

DY was higher in MW (63.8%, *n* = 81) than PMW (30.4%, *n* = 17), and post-menopausal status was significantly associated with higher DY (*P* < 0.001).

Table 4 Capsule endoscopy outcomes in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Diagnostic yield	98 (53.6)	17 (30.4)	81 (63.8)	< 0.001
Therapeutic yield	23 (12.6)	1 (1.8)	22 (17.3)	0.003
Rebleeding rate	46 (25.1)	5 (8.9)	41 (32.3)	0.031
Time to rebleed, yr				0.001
	1 yr, 16.4	1 yr, 3.6	1 yr, 22.0	
	3 yr, 25.8	3 yr, 10.2	3 yr, 32.3	
	5 yr, 27.2	5 yr, 10.2	5 yr, 34.2	
Hospitalization rate	13 (7.1)	1 (1.8)	12 (9.4)	0.063
Mortality rate	2 (1.0)	0 (0)	2 (1.6)	0.345

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance.

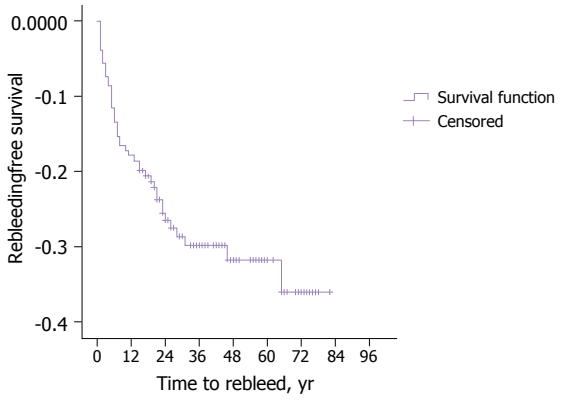

Figure 2 Kaplan-Meier curves according to the time to rebleed.

TY was significantly higher in MW (17.3%, *n* = 22) compared to PMW (1.8%, *n* = 1) (*P* = 0.003).

The rebleeding rate was significantly higher in MW (*P* = 0,031). Considering a follow-up period of 1, 3 and 5 years, MW had a significantly higher rebleeding rate (MW 22.0%; 32.3%; 34.2% *vs* PMW 3.6%; 10.2%; 10.2%) (*P* = 0.001) (Table 4 and Figure 3).

In the MW group hospitalization due to OGIB was higher (MW-9.4%, PMW-1.8%). Mortality due to OGIB in MW was 1.6%, and there was no death in PMW. There was no significant differences between groups concerning hospitalization (*P* = 0.063) and mortality (*P* = 0.345).

DISCUSSION

OGIB, particularly IDA is the most frequent indication (66%) for CE study[20]. Several studies on the DY of CE in IDA were performed. A systematic review from Koulaouzidis *et al*[21] showed a pooled CE DY for detection of small bowel findings of 46%. The literature on CE findings and DY in MW and PMW is sparse and in fact evidence from CE DY in OGIB is heterogeneous and lies in two types of study designs: those specifically designed to evaluate the role of CE in patients with IDA and those that investigated patients with a wider range of indications including overt GI bleeding.

In our study, the DY of CE in MW was significantly higher compared to PMW. TY and the rebleeding rate were also higher while time to rebleed was lower in female patients with post-menopausal status. A retrospective study of Garrido-Durán *et al*[15] documented a DY of CE of 55.0% and 13.7% in MW and PMW respectively. More recently a multicentric retrospective study from Perrod *et al*[10] obtained similar results, with 34.0% for MW and 15.0% for PMW. These results do not substantially differ from our data, regarding DY of CE in OGIB. Nor Garrido-Duran's nor Perrod's studies evaluated TY, rebleeding, time to rebleed, hospitalization nor mortality. In our study MW had more frequently small bowel lesions eligible for endoscopic treatment. There is quite sparse literature in the TY of CE, the rebleeding rate and time to rebleed due OGIB in females comparing pre and post menopause periods. Nevertheless those variable were extensively studied in patients submitted to CE[13,18,19,22,23]. The fact that MW had a higher rate of comorbidities and consumption of anticoagulants, antiplatelet and NSAIDs may partially explain the higher DY, TY and rebleeding rate.

Angiodysplasias were the main findings in CE studies of both groups. Previously published papers comparing PMW and MW had the same outcomes[10,15].

The main achievement of the present study is to bring to evidence the poor results of OGIB investigation through CE in PMW, making clear the need of exclusion of gynecological pathology in this subset of patients[24]. In this population, IDA is often related to gynecological symptoms and gastrointestinal lesions are diagnosed in less than 20% after endoscopic explorations[25].

The present study has some limitations. It has a retrospective design with a small number of patients, therefore a prospective assessment of CE DY in females before and after menopause is warranted. The patients enrolled in the present study were not assessed in a Gynecology appointment in order to confirm menopause diagnosis.

In conclusion PMW with suspected OGIB are less likely to have significant findings in CE. The lower rates of positive findings may be related to gynecological comorbidities, which must be previously excluded. In this group the DY, TY and rebleeding were significantly lower while time to rebleed was higher.

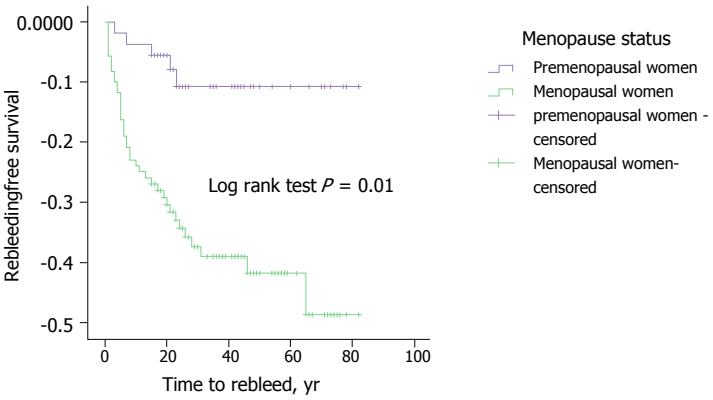

Figure 3 Kaplan-Meier curves according to the time to rebleed between premenopausal and menopausal women.

ARTICLE HIGHLIGHTS

Research background

Findings of capsule endoscopy (CE) for obscure gastrointestinal bleeding (OGIB) investigation performed in females may vary substantially according to menopause status. In this paper we estimated and compared diagnostic yield (DY) of CE as well as its therapeutic yield (TY) and clinical outcomes in premenopausal women (PMW) and menopausal women (MW).

Research motivation

Negative CE may lead to increased health costs and delayed diagnosis when performed in patients who were not fully investigated, as OGIB is an exclusion diagnosis.

Research objectives

To compare the DY of CE for OGIB study and correlated this outcome with menopause presence.

Research methods

The DY, TY, rebleeding rate, hospitalization and mortality were calculated and compared according to menopausal status.

Research results

Postmenopausal age was associated with higher DY, need for endoscopic treatment, rebleeding, and hospitalization.

Research conclusions

PMW with suspected OGIB is less likely to have significant findings in CE. This suggests that fertile age women should be carefully studied, preferably by a multidisciplinary approach, before CE.

Research perspectives

Our study has a retrospective design with a small number of patients, so a prospective comparative assessment of CE findings between PMW and MW with a larger population is warranted. In addition routine evaluation by a Gynecologist may reduce the negative CE burden.

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P- Reviewer: Cui J, Huang LY, Naito Y **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Wu YXJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2018 October 16; 10(10): 308-321

DOI: 10.4253/wjge.v10.i10.308

ISSN 1948-5190 (online)

SYSTEMATIC REVIEW

Systematic review of safety and efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography during pregnancy including studies of radiation-free therapeutic endoscopic-retrograde-cholangiopancreatography

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Author contributions: Cappell MS had the most important contributions to the organization, writing, and editing of the manuscript; Stavropoulos SN and Friedel D contributed very significantly to all aspects of the paper, including the organization, writing, and editing of the manuscript; the final manuscript was reviewed, corrected, and approved by all three authors.

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

Manuscript source: Invited manuscript

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Received: April 28, 2018
Peer-review started: April 28, 2018
First decision: May 18, 2018
Revised: July 13, 2018
Accepted: August 26, 2018
Article in press: August 27, 2018
Published online: October 16, 2018

Abstract

AIM

To systematically review safety/efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography (ERCP) performed during pregnancy, considering fetal viability, fetal teratogenicity, premature delivery, and future postpartum development of the infant.

METHODS

Systematic computerized literature search performed using PubMed with the key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus and preassigned priorities. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports were assigned lowest priority. Dr. Cappell has formal training and considerable experience in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a PhD in neurophysiology that involved 5 years of training and research in biomedical statistics.

RESULTS

Advances in imaging modalities, including abdominal ultrasound, MRCP, and endoscopic ultrasound, have generally obviated the need for diagnostic ERCP in non-pregnant and pregnant patients. Clinical experience with performing ERCP during pregnancy is burgeoning, with > 500 cases of therapeutic ERCP reported in the literature, aside from a national registry study of 58 patients. These studies show that therapeutic ERCP has a very high rate of technical success in clearing the bile duct of gallstones, and has a relatively low and acceptable rate of maternal and fetal complications. The great majority of births after therapeutic ERCP are full-term, have normal birth weights, and are healthy. A recent trend is performing ERCP without radiation to eliminate radiation teratogenicity. Systematic literature review reveals 147 cases of ERCP without fluoroscopy in 8 clinical series. These studies demonstrate extremely high technical success in endoscopically removing choledocholithiasis, favorable maternal outcomes with rare maternal ERCP complications, and excellent fetal outcomes. ERCP without fluoroscopy generally confirms proper biliary cannulation by aspiration of yellow bile per sphincterotome or leakage of yellow bile around an inserted guide-wire.

CONCLUSION

This systematic literature review reveals ERCP is relatively safe and efficacious during pregnancy, with relatively favorable maternal and fetal outcomes after ERCP. Recommendations are provided about ERCP indications, special ERCP techniques during pregnancy, and prospects for future research.

Key words: Minimally invasive therapy; Endoscopy; Ascending cholangitis; Therapeutic endoscopic-retrograde-cholangiopancreatography; Pregnancy; Radiation teratogenicity

Core tip: This work systematically reviews safety/efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography (ERCP) performed during pregnancy, considering fetal viability, fetal teratogenicity, premature delivery, and future development of the infant after parturition. Systematic computerized literature search was performed using PubMed with key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on pre-arranged prioritization and consensus. Clinical experience with performing ERCP during pregnancy is burgeoning, with > 500 cases of therapeutic ERCP reported in the literature, plus a national registry study of 58 patients.

Cappell MS, Stavropoulos SN, Friedel D. Systematic review of safety and efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography during pregnancy including studies of radiation-free therapeutic endoscopic-retrograde-cholangiopancreatography. *World J Gastrointest Endosc* 2018; 10(10): 308-321 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/308.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.308

INTRODUCTION

Endoscopic-retrograde-cholangiopancreatography (ERCP) is currently the standard technique for treating choledocholithiasis and associated complications, such as cholangitis and biliary stricture, in the non-pregnant population. The approach to pregnant women with suspected choledocholithiasis, however, differs somewhat from that for non-pregnant patients because of concerns about the pregnant mother and the fetus, including procedure time, teratogenicity of intra-procedural medications, and fetal radiation exposure. This work systematically reviews ERCP during pregnancy, with a particular focus on differences between the pregnant *vs* non-pregnant patient in patient indications, patient preparation, procedural medications, complications, reducing fetal radiation exposure, and maternal and fetal outcomes.

MATERIALS AND METHODS

Systematic computerized literature search was performed using PubMed with the key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports were assigned the lowest priority. Data were extracted independently by 2 authors to prevent errors in data extraction. Dr. Cappell has formal training and considerable experience in conducting in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a Ph.D. in neurophysiology that involved 5 years of training and research in biomedical statistics.

RESULTS

Pathophysiology of cholelithiasis and choledocholithiasis

Up to 20% of American adults have cholelithiasis, of whom about 20% develop symptoms or complications during their life-time[1,2]. About 750000 cholecystectomies are performed annually in America. Risk factors for cholelithiasis include advanced age, female gender, obesity, hyperlipidemia, pregnancy, and physical inactivity[2]. Symptoms and complications increase in frequency when gallstones are present > 5 years, and when they are > 10 mm in diameter[3]. The pathophysiology of pregnancy-related lithogenicity includes bile super-

saturated with cholesterol, increased gallbladder volume, diminished gallbladder motility, and changes in the bile salt pool[4-7]. These gestational changes are largely mediated by increased levels of the gestational hormones of estrogen and progesterone[4].

Epidemiology

The prevalence of cholelithiasis during pregnancy varies with the study population. A study performed in India noted only a 1% prevalence[8], whereas a study performed in a Californian Hispanic cohort reported a 5% prevalence[9]. Both cohorts were asymptomatic at study initiation. A prospective study of abdominal ultrasound among > 3000 pregnant subjects without cholelithiasis detected at baseline showed 5% developed cholelithiasis by the second trimester, and 10% developed cholelithiasis by six weeks postpartum[10]. About 1% of this cohort developed symptoms from cholelithiasis. A Mexican study noted that symptomatic gallstone disease during pregnancy usually manifests as acute cholecystitis, even though 19% had choledocholithiasis[11]. Cholelithiasis and hypertriglyceridemia are the primary etiologies of pancreatitis during pregnancy[12,13], whereas alcohol-induced pancreatitis is unusual during pregnancy because expectant mothers generally abstain from alcohol due to its fetal toxicity[14]. Cholelithiasis and choledocholithiasis are sometimes encountered during pregnancy because female gender, concurrent pregnancy, and prior pregnancy are risk factors for cholelithiasis. Fortunately, the endoscopist is infrequently required to perform ERCP, with its attendant risks during pregnancy, because ERCPs can often be delayed to postpartum because patients have minimal clinical findings or can directly undergo cholecystectomy without antecedent ERCP for acute cholecystitis.

Special concerns and modifications of ERCP during pregnancy

The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. ERCP in non-pregnant patients is usually performed with the patient in the prone position to aid in selective bile cannulation and to provide better fluoroscopic imaging compared to other positions. However, this position is not recommended during advanced pregnancy for the following reasons: to avoid patient discomfort from the enlarged, gravid uterus pressing against the hard X-ray platform, to avoid decreased systemic and uterine perfusion from the enlarged gravid uterus compressing the aorta, and to avoid decreased venous return from the enlarged gravid uterus compressing the inferior vena cava[15]. Patients may also require supporting cushions during advanced pregnancy to minimize patient discomfort. Rapid intra-procedural infusion of Ⅳ fluids is generally recommended to promote pancreatic perfusion and decrease the incidence and severity of post-ERCP pancreatitis, but may be inadvisable during pregnancy because of the already expanded extravascular space and salt retention during pregnancy[16]. However, the fetus poorly tolerates maternal systemic hypotension because blood flow is shunted away from the uterus during maternal hypotension[17], and maternal hypotension should, therefore, be aggressively treated, if feasible, before performing ERCP. As for all patients undergoing ERCP, the pregnant patient should have her vital signs stabilized, electrolyte disorders corrected, and major disorders such as sepsis, hypovolemia, and hypoxemia addressed before undergoing ERCP. As in the general population all pregnant patients undergoing anticipated therapeutic ERCP should have a complete hemogram and prothrombin/international normal ratio determination. It is important to test for pregnancy with a beta-HCG determination in women who are undergoing ERCP, are of childbearing age, and have a recent pregnancy history that is uncertain or suggestive of early pregnancy to avoid inadvertent fetal radiation exposure[18].

The mother should be maintained nil per os (NPO) for at least 6 h before ERCP to reduce risks of aspiration of gastric contents. Elective endotracheal intubation should be strongly considered before ERCP, especially during advanced pregnancy, because the gravid uterus, impinges upon the stomach and increases the risk of aspiration of gastric contents[19]. It may, moreover, be necessary to perform ERCP in the supine position, especially during advanced pregnancy, which can further increase aspiration risks[20]. The mother can typically be extubated soon after ERCP in the absence of chronic pulmonary disease.

The American Society for Gastrointestinal Endoscopy promulgated guidelines for endoscopy during pregnancy, including ERCP, which incorporate safety data for commonly used endoscopic medications during pregnancy[21,22], as classified by the United States Food and Drug Administration (FDA) from A (most safe) to D (least safe), with a special category of X, for drugs contraindicated during pregnancy. The general principle is to avoid FDA category X and restrict FDA category D drugs, and substitute FDA category B or C drugs for category D drugs, if feasible, during pregnancy. Indomethacin suppositories are recommended for ERCP in patients at risk for pancreatitis, but indomethacin is an FDA category C drug, with concern about premature closure of a patent ductus arteriosus (PDA) in late pregnancy[22]. Propofol is considered safe (FDA category B), even though it crosses the placenta and causes transient fetal sedation. Meperidine is considered safer (FDA category B) than either fentanyl or morphine (both FDA category C). Moreover, meperidine causes minimal spasm of the sphincter of Oddi, whereas other narcotics may cause problematic spasm of this sphincter during ERCP. Midazolam is considered safer than diazepam, even though both are category D drugs because diazepam has been occasionally associated with cleft palate[23].

Table 1 General principles of endoscopic retrograde cholangiopancreatography during pregnancy

1. Counsel patient, husband, and family on risks vs benefits of ERCP for mother as well as fetus
2. Obtain written informed consent from pregnant patient (not the father)
3. Endoscopist should assess whether his/her experience and skill is adequate for dealing with anticipated biliary pathology in a pregnant patient with this medical history
4. Position patient on left side or supine, if possible, especially during advanced pregnancy
5. Preferentially perform ERCP during second trimester, if possible
6. During late third trimester, delay elective ERCP to after delivery
7. Use safety guidelines (see Table 2) to minimize fetal radiation exposure and risks
8. Consider performing EUS prior to ERCP to assess CBD diameter as well as number, size, and shape of gallstones
9. Multidisciplinary input involving a perinatologist, high-risk obstetrician, obstetric anesthesiologist, radiation safety officer, and surgeon prior to ERCP
10. Administer parenteral fluids consistent with clinical status and pregnancy requirements
11. Reverse metabolic derangements and appropriately intervene to correct abnormalities in vital signs before scheduling ERCP
12. Administer antibiotics and other drugs during ERCP that are considered relatively safe during pregnancy
13. Endoscopist should be familiar with and prepared to use full armamentarium of endoscopic techniques including needle-knife sphincterotomy, transeptal sphincterotomy, choledochoscopy, and IDUS
14. Counsel patients regarding requirements for follow-up visits, especially with stent placement
15. Avoid pancreatic endotherapy during ERCP because this entails a higher risk than biliary endotherapy

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; CBD: Common bile duct; IDUS: Intraductal ultrasound.

Glucagon is used to reduce intestinal spasm and is believed to be generally safe during pregnancy (FDA category B)[24]. Glucagon administration may be justifiable during ERCP if needed to cannulate the choledochus during therapeutic ERCP to prevent maternal cholangitis from choledocholithiasis, but glucagon administration can usually be obviated by prompt choledochal cannulation by an expert endoscopist. Simethicone is used to eliminate troublesome intraluminal bubbles and is believed to be relatively safe during pregnancy (FDA category C)[25]. It should, however, be used only if necessary during ERCP. Informed patient consent for ERCP should include a discussion regarding fetal safety during pregnancy, including fetal toxicity from radiation exposure. In terms of antibiotics, penicillins/cepholosporins/macrolides are generally safe, provided no hypersensitivity occurs, but quinolones/tetracyclines/sulfonamides/Flagyl are not safe[25].

The management of pregnant women with pancreaticobiliary disease requires a multidisciplinary approach, with a clinical team including a gastroenterologist, obstetrician/perinatologist, radiation safety officer, and anesthesiologist, who preferably specializes in obstetric anesthesiology. The requisite experience and expertise is typically found in a tertiary, academic medical center. The gastroenterologist should have significant expertise and experience in ERCP to be best equipped to deal with the challenges and risks of ERCP during pregnancy. The qualifications of an experienced advanced therapeutic endoscopist have not been standardized, but may include both a > 90% bile duct cannulation rate[26], and an adequate annual volume of therapeutic ERCPs (> 40 sphincterotomies per year)[27]. One study demonstrated that low volume ERCP-endoscopists exposed their patients to significantly more radiation during ERCP than high volume ERCP-endoscopists[28]. An experienced endoscopist is more likely to minimize procedural time, anesthesia dosages, and radiation time. An inexperienced gastroenterology fellow should play a limited role in this situation. The anesthesiologist should be in attendance during the entire ERCP, and not rely on a nurse anesthetist for administering sedation. The surgeon plays a critical role in the timing of cholecystectomy, and in providing backup for emergency CBD exploration or for complications after ERCP[29].

Electrocautery is a concern during pregnancy. Amniotic fluid readily conducts electricity which can reach the fetus[21,30]. Biliary sphincterotomy should use only bipolar current to decrease scatter of electricity. Biliary sphincterotomy, if necessary during ERCP, should use minimal cautery with the grounding pad placed on the right side, such as the right arm or right posterior thorax, to minimize electrical conduction to the fetus[22,31]. Strategies to avoid electrocautery include inserting a biliary stent without cautery, but this can be problematic unless delivery is imminent because of a long-term potential for stent clogging. Balloon sphincteroplasty is an alternative to sphincterotomy, but this maneuver can induce pancreatitis[32]. General principles of ERCP during pregnancy are summarized in Table 1.

Fetal radiation exposure is a significant concern because of its potential teratogenic effects and subsequent carcinogenetic effects. Fetal radiation exposure and toxicity depends upon multiple factors, including maternal size, maternal distribution of fat, volume of amniotic fluid, fetal gestational age, and radiation delivery method. The most important factors determining fetal exposure are total radiation time and dosage, both of which should be minimized. Draping the lower abdomen and pelvis of patients with lead shields helps minimize uterine exposure[21]. Lead shielding is best placed below the patient because radiation typically emanates from below[21]. However, radiation scatter within the mother is likely the main source of fetal radiation exposure[33]. Static (spot) films are recommended instead of continuous fluoroscopy to decrease radiation exposure[34]. Also recommended are a modern radiation source, a well collimated unit, and avoidance of "hard-copy" images

Table 2 Maximizing radiation safety of endoscopic retrograde cholangiopancreatography during pregnancy

1. Highly qualified and experienced ERCP endoscopist
2. Limited (solely observational) role of inexperienced gastroenterology fellow during ERCP
3. Informed consent to include discussion of radiation teratogenicity
4. Consult perinatologist
5. Consult radiation safety officer and medical physicist, if available, to minimize fetal radiation exposure
6. Endoscopist performing ERCP should become familiar with fluoroscopy equipment, especially with options to minimize radiation exposure
7. Formal consultation of anesthesiologist before ERCP
8. Anesthesiologist to attend during entire ERCP, even if nurse-anesthetist is present
9. Consider using an obstetric anesthesiologist rather than a general anesthesiologist for ERCP
10. Avoid ERCP for weak indications
11. Avoid solely diagnostic ERCP
12. Strongly consider MRCP as an alternative for diagnostic ERCP in low yield indications
13. Obtain informed, written consent that includes discussion of risks of fetal radiation
14. Perform ERCP at a hospital endoscopy unit rather than an ambulatory center in order to better manage procedural complications
15. Perform ERCP at a tertiary hospital rather than a community hospital where highly specialized consultants are likely to be present
16. Perform ERCP as expeditiously as possible to minimize radiation exposure and anesthesia medications
17. Employ modern and highly collimated radiation unit with the smallest possible field
18. Position patient as far as possible from radiation source consistent with reasonable images
19. If possible, employ "low-dose" radiation protocol in terms of kvp, field size, and frame rate
20. Place lead shield underneath patient between likely fetal area and radiation tube
21. Place dosimeters on patient above expected uterine location and record fluoroscopy time and total radiation dosage
22. Minimize procedure time, procure all anticipated endoscopy equipment within endoscopy room before beginning the procedure
23. Employ static images as opposed to continuous fluoroscopy to reduce radiation exposure
24. Use digital image acquisition technology if possible, instead of film-screen radiography
25. Position patient to permit anterior-posterior beam projection
26. Avoid image magnification
27. Employ last image-hold or fluoroscopy loop recording feature when possible rather than additional fluoroscopy
28. Consider radiation-free ERCP in conjunction with other techniques such as temporary stenting and, if needed, needle-knife and transpapillary sphincterotomy
29. Document ductal clearance without radiation using IDUS or choledochoscopy
30. X-ray image receptor should be placed as close as possible to the patient
31. Adjust patient position between choices of supine, prone, or lateral to minimize fetal radiation exposure

ERCP: Endoscopic retrograde cholangiopancreatography; kVp: Peak kilovoltage; IDUS: Intraductal ultrasound.

that require higher radiation dosage[21]. A radiation safety officer can provide valuable input. Dosimetry monitors can be placed externally on top of the uterus to monitor fetal radiation exposure. In one case, this device demonstrated low radiation exposure to the fetus, and higher radiation exposure to the maternal placenta and spleen[35]. Radiation exposure often exceeds 10 millisievert (mSv) during prolonged ERCP[33]. With recommended precautions, fetal radiation exposure during ERCP should be uniformly < 50-100 mSv, which is considered the radiation threshold for teratogenesis[21,36]. Techniques to reduce radiation exposure are summarized in Table 2.

Fetal radiation exposure is particularly concerning during early pregnancy. Radiation exposure to > 200 mGy could result in growth restriction and congenital anomalies, especially of the eyes, skeleton, and genitalia[31]. Thus, semi-elective ERCP should be deferred to the second trimester when feasible. Untoward outcomes of ERCP–related radiation exposure is not well studied, and they may conceivably manifest only later in childhood. Regardless, radiation exposure should be well documented, if feasible, for retrospective analysis[37]. One study suggested this documentation was unnecessary because of low teratogenicity risk, but this study used limited fluoroscopy time[38].

Outcomes and complications of therapeutic ERCP during pregnancy

Outcome analysis regarding ERCP during pregnancy should consider technical procedural success, fetal outcomes, neonatal health, and birth weight. In a relatively large, retrospective, study of 68 ERCPs during 65 pregnancies, technical success was uniformly achieved[39]. Although 11 patients (16%) developed pancreatitis after ERCP, no other major complications occurred, including maternal hemorrhage, gastrointestinal perforation, or ascending cholangitis; maternal or fetal deaths; and fetal malformations. ERCPs performed during the first trimester had relatively worse fetal outcomes. Fifty-three patients (90%) had a full–term pregnancy after ERCP, but mothers undergoing ERCP during the first trimester had only 73% of deliveries at term, a higher risk of preterm delivery (20%), and higher risk of low-birth-weight infants (21%). In a series of 20 patients undergoing therapeutic ERCPs during pregnancy, there was one neonatal death 26 h after delivery that occurred in a patient who had undergone three therapeutic ERCPs during pregnancy with pancreatic duct stenting at each session for pancreatic duct stenosis after surgical sphincteroplasty[15]. This patient had developed acute pancreatitis after each of her 3 ERCPs. Another mother suffered spontaneous abortion 3 wk

after ERCP. There were no other significant maternal or fetal complications.

A national cohort study of 58 pregnant women undergoing ERCP *vs* a three-fold larger control population of non-pregnant women demonstrated that the major ERCP complications of gastrointestinal perforation, hemorrhage, or infection were not more common during pregnancy, but post-ERCP pancreatitis was significantly increased during pregnancy at 12% *vs* 5% (adjusted odds ratio: 2.8, 95%CI: 2.1-3.8). This increased rate is attributed to avoiding fluoroscopy to verify wire and catheter position and to time pressure to expeditiously perform ERCP during pregnancy[40-42]. This work is important in that it represents the largest study heretofore on ERCP during pregnancy, but is subject to limitations including lack of data on patient comorbidities, maternal alcohol or illicit drug use, endoscopic complications, type of ERCP (diagnostic *vs* therapeutic), ERCP indications, and use or lack of monitored anesthesia care[43]. Also, as aforementioned, usual measures to minimize pancreatitis after ERCP, such as high volume IV fluid infusion, indomethacin suppositories, and pancreatic stents are infrequently used during pregnancy. A recent large, multicenter, study demonstrated that endoscopy during pregnancy is associated with an increased risk of preterm birth or small size for gestational age, but no increased risk of stillbirths or congenital malformations[40-42].

In a series of 18 women undergoing ERCP with biliary sphincterotomy for choledocholithiasis, one patient had a postsphincterotomy bleed and one patient had mild pancreatitis after ERCP and had preterm labor, but fetal outcomes were all favorable[44]. Scant data exist on long term postpartum follow-up after intrapartum ERCP, but this study of 18 women reported normal child development at 6 years[44]. Generally, therapeutic ERCP is believed to be relatively safe and effective during pregnancy, though safety concerns are increased during the first trimester, and there appears to be an increased risk of maternal pancreatitis after ERCP during pregnancy.

Two relatively large systematic reviews, one published in full[45], and the other published as an abstract[46], show that ERCP during pregnancy is relatively safe. In a systematic literature review performed by Cappell in 2011[45], 296 pregnant patients underwent therapeutic ERCP. Fetal outcomes as reported in 254 cases (86%) included: healthy infants at birth in 237, prematurely born infants with low birth weight in 11, late spontaneous abortions in 3, infant death soon after birth in 2, and voluntary abortion in 1. Perinatal mortality was only about 1% despite pregnant mothers undergoing therapeutic ERCP mostly for major gallstone complications, such as obstructive jaundice, ascending cholangitis, or gallstone pancreatitis. Moreover, no congenital anomalies were reported in the infants. However, these very favorable outcomes must be interpreted cautiously because most of the reviewed studies reported outcome only at parturition without subsequent follow-up, and fetal outcome data was absent in 15% of the pooled study patients.

A systematic literature review of 214 ERCP's during pregnancy, published only as an abstract, reported a 5% pancreatitis rate, a 5% preterm birth rate, and about a 1% rate of spontaneous abortions[46]. Technical success of ERCP was high, even though >10% had to undergo stent placement and/or multiple ERCPs. These data on the largest individual studies and prior systematic reviews are summarized in Table 3.

DISCUSSION

Recommendations

In the general population solely diagnostic ERCP is not recommended anymore, and has been replaced by less invasive tests such as endoscopic ultrasound (EUS); and magnetic resonance cholangiopancreatography (MRCP)[47]. ERCP is not recommended unless it is most likely to be therapeutic. The same principle applies during pregnancy: solely diagnostic ERCP is not recommended during pregnancy.

During the past 30 years, therapeutic ERCP during pregnancy has evolved from a novelty described in case reports to accepted practice with refinement of endoscopic techniques paralleling greater clinical experience, better technology, and greater technical expertise[21,31,48-51]. Progress in ERCP has been paralleled by advances in laparoscopic cholecystectomy. The first ERCP during pregnancy was a report in 1990 of five successful cases of biliary sphincterotomy and gallstone extraction for choledocholithiasis or cholangitis[48]. An estimated 500 or more women have been reported undergoing ERCP during pregnancy, aside from a national registry study of 58 patients[42]. Considerations in performing ERCP during pregnancy include clinical indication, maternal clinical status, laboratory results, ancillary radiologic studies, fetal age, endoscopist expertise, and hospital support. Risks *vs* benefits should be assessed for every high risk endoscopic procedure during pregnancy, especially ERCP[45]. Patients with documented choledocholithiasis associated with gallstone pancreatitis, cholangitis, jaundice, significant abdominal pain, pyrexia, leukocytosis, common bile duct dilatation on imaging studies, or grossly abnormal liver function tests need urgent ERCP, just like non-pregnant patients[52]. Patients with significantly elevated liver enzymes and/or a dilated CBD are more likely to harbor choledocholithiasis than patients without these features[53]. Preoperative ERCP is preferred over the alternative of direct cholecystectomy for these indications to avoid the increased morbidity and mortality from complex biliary surgery during cholecystectomy[54]. However, the indication for ERCP is more ambiguous in minimally symptomatic or asymptomatic patients with choledocholithiasis. Evaluation and therapy for uncomplicated cholelithiasis discovered during pregnancy is generally deferred until postpartum. Most patients with acute cholecystitis during pregnancy undergo cholecystectomy without preoperative ERCP[55]. Indeed. cholecystectomy for acute cholecystitis is the third most

Table 3 Literature review of relatively large clinical studies on safety of endoscopic retrograde cholangiopancreatography during pregnancy

First author, yr, reference	Study characteristics	Findings
Tang SJ, 2009[39]	Large retrospective study of 68 ERCPs performed during 65 pregnancies.	Pancreatitis occurred in 11 pregnant patients (16%) after ERCP. No other major maternal complications occurred during pregnancy. No fetal deaths and no fetal malformations occurred. After ERCP 53 patients had deliveries at term (90% rate for known delivery outcomes). However, ERCP performed during first trimester had less favorable outcomes: preterm delivery = 20%, and low-birth-weight infants = 21%
Ludvigsson JF, 2017[42]	National cohort study in Sweden of 58 pregnant patients undergoing ERCP included in a much larger study of 3052 patients undergoing any gastrointestinal endoscopy during pregnancy.	Of 58 pregnant patients undergoing ERCP unfavorable fetal outcomes included: 3 (5.2%) preterm births, 0 (0%) stillbirths, 0 (0%) neonatal deaths, 12 (20.7%) Cesarean sections, 1 (1.7%) Apgar score < 7 at 5 min, 1 (1.7%) small for gestational age, and 3 (5.2%) with any major congenital malformation. All these pregnancy outcomes were similar to that of pregnancy outcomes for mothers not undergoing endoscopy during pregnancy
Jamidar PA, 1995[15]	Retrospective study of therapeutic ERCPs performed during 20 pregnancies.	Two significant complications: one spontaneous abortion 3 wk after ERCP, and 1 neonatal death 26 h. post-partum that occurred after the expectant mother underwent 3 therapeutic ERCPs during pregnancy with pancreatic stenting at each session complicated by post-ERCP pancreatitis. No other significant maternal or fetal complications
Gupta R, 2005[44]	Retrospective study of therapeutic ERCPs performed during 18 pregnancies for choledocholithiasis.	Complications: 1 mild postsphincterotomy bleed; and 1 mild pancreatitis and preterm labor after ERCP. All fetal outcomes were favorable. This study had long-term follow-up after intra-partum ERCP: all 18 infants had normal child development at 6 yr
Cappell MS, 2011[45]	Systematic literature review of 296 pregnant patients undergoing therapeutic ERCP including 254 (86%) in which fetal outcome was reported.	Fetal outcomes as reported in 254 cases included: healthy infants at birth in 237, prematurely born infants with low-birth-weight in 11, late spontaneous abortions in 3, infant death soon after birth in 2, and voluntary abortion in 1. Perinatal mortality was only about 1% despite pregnant mothers undergoing therapeutic ERCP mostly for major gallstone complications, such as obstructive jaundice, ascending cholangitis, or gallstone pancreatitis. No congenital anomalies were reported in the infants. These favorable data must be interpreted cautiously: in this literature review, fetal outcome data were missing in 42 (15%) of reported mothers undergoing ERCP during pregnancy

ERCP: Endoscopic retrograde cholangiopancreatography.

common non-obstetric operation performed during pregnancy[56].

The diagnostic armamentarium for suspected choledocholithiasis in pregnancy differs from the general approach in non-pregnant patients in that radiation-based imaging, such as abdominal CT, is not employed. Transabdominal ultrasound is relatively inexpensive and safe during pregnancy and is typically the initial imaging test. MRCP is especially useful during pregnancy, but raises a concern about a negative exam in the face of disparate clinical and laboratory findings[57]. In one small series, MRCP obviated the need for ERCP in pregnant women with pancreatobiliary abnormalities[58]. EUS is safe in pregnancy and highly accurate, but commits the patient to an endoscopy during pregnancy with its inherent procedural and sedation risks. However, a negative EUS examination can obviate ERCP with its greater attendant risks[59]. EUS also provides data on number, size, location, and morphology of choledocholithiasis for patients requiring ERCP.

Pregnancy stage and fetal development are paramount considerations in the timing of ERCP. ERCPs and cholecystectomies are generally best performed during the second trimester, after organogenesis during the first trimester and before the third trimester with its increased risk of premature delivery[45,60]. Postpartum ERCP is the best option if delay is feasible.

The prospect of ERCP often promotes anxiety in both the mother and endoscopist. Recent studies still show some risks of ERCP during pregnancy[48,61]. The large series by Tang *et al*[39] reported that ERCP can be safely performed throughout pregnancy, but may somewhat impact fetal health when performed during early gestation. An early multicenter series, including 15 first trimester ERCPs (FTE), demonstrated technical success, but had complications of one spontaneous abortion and one neonatal death[15]. Another series with dedicated obstetric input and lead shielding demonstrated good technical success and good fetal outcome, though only one FTE was performed[62]. An Indian series had 4 FTE's, trivial fluoroscopy time, and a six year child follow-up[46]. The two series by Smith *et al*[38] and Kahaleh *et al*[63] were notable for limited fluoroscopy time, technical success, and good fetal outcomes, though two women developed eclampsia during the third trimester after undergoing ERCP. These series noted a slightly higher rate of post-ERCP pancreatitis than in the general population, in accord with cumulative data[40,41].

Most studies of ERCP during pregnancy are limited by relatively small study size, absence of controls,

Table 4 Literature review of case series of radiation-free endoscopic retrograde cholangiopancreatography during pregnancy

First author, yr, reference	Number reported	Indications	Technique of radiation-free ERCP	Outcomes
Shah 2016[75]	Non-radiation ERCP attempted-31 non-pregnant subjects. 26 successfully underwent ERCP without fluoroscopy. 5 required fluoroscopy during ERCP	Adult patients with suspected biliary stones based on abnormal serum liver tests, abdominal imaging, and/or abdominal pain. Underwent EUS per protocol. Patients with suspected large stone burden, complicated stone disease, or difficult anatomy were excluded	Antecedent EUS used as a guide before ERCP. Selective cannulation confirmed by aspirating visible bile in 26 patients. 5 patients required radiation for double wire or precut papillotomy. All patients had EUS. 4 others had ERCP obviated by EUS	No adverse events among patients who underwent bile cannulation, sphincterotomy, and stone removal without fluoroscopy. One patient undergoing ERCP with fluoroscopy had moderated post-ERCP pancreatitis
Ersoz 2016[74]	22 patients: first trimester-2, second trimester-3, third trimester-17	Abdominal ultrasound demonstrates stone/sludge in gallbladder-22 (100%), choledocholithiasis-12, mean total bilirubin = 5.49 ± 1.66 mg/dL, acute cholangitis-2, acute cholecystitis-2	Selective biliary cannulation attempted with sphincterotome and confirmed by bile aspiration. Biliary sphincterotomy and balloon dilation-18/22 had visible gallstones, 3 required transpancreatic papillary septotomy	5 complications after ERCP: epigastric pain without elevated lipase elevation-2, mild pancreatitis treated conservatively-2, minor post-sphincterotomy bleeding successfully treated with epinephrine injection without blood transfusions. All delivered healthy infants at term
Sethi S, 2015[73]	3 patients: 14, 7, or 28 wk pregnant	1 and 2-Dilated CBD and total bilirubin > 5.0 mg/dL after laparoscopic cholecystectomy, 3-Dilated CBD, multiple gallstones and increased total bilirubin level	All cases: EUS-guided ERCP with selective biliary cannulation confirmed by bile aspiration. Biliary sphincterotomy and stone extraction(s) using balloon sweeps or Spyglass technology	Uncomplicated. All mothers did well-rapidly discharged from hospital. Fetal outcomes not reported
Agcaoglu O, 2013[72]	5 patients: mean gestational age = 20 wk, range 12-32 wk	Gallstone pancreatitis and obstructive jaundice-3, cholangitis and obstructive jaundice-2	Selective cannulation confirmed by aspiration or direct visualization of bile. After CBD cannulated guide-wire passed, sphincterotomy completed, and stones extracted by basket or balloon sweep	No maternal or fetal adverse events or short term complications. No long-term follow-up available
Yang J, 2013[71]	24 patients: first or second trimester-9, third trimester-15	All patients had severe biliary pancreatitis. Leukocyte count 15000-29000 × 10^6/L, serum amylase: 500-2000 units/L, increased bilirubin in 20	All patients underwent emergency ERCP without fluoroscopy and endoscopic biliary drainage. 15 patients in third trimester had pregnancy terminated: induced delivery-7, cesarean section-6, full-term normal delivery-2. Then underwent second ERCP with fluoroscopy to remove gallstones. 9 patients in early pregnancy underwent endoscopic retrograde biliary drainage in second ERCP without fluoroscopy. Had biliary stent for average of 3.8 mo	100% technical success rate: CBD stones removed in all 24 patients. Only 2 maternal complications: mild hemorrhage during second ERCP. All infants born healthy. At term births-20, premature births-4 with cesarean section (for severe intrauterine distress)
Huang P, 2017[70]	86 patients (largest series): no fluoroscopy-81 ultra-short duration of fluoroscopy-5. Mean gestational age = 22.5 wk, Range: 15-35 wk	Acute biliary pancreatitis-32, acute cholangitis-23, dilated CBD-20, severe nonbiliary acute pancreatitis-11	Underwent antecedent abdominal ultrasound or MRCP. CBD cannulated using a guide-wire and then catheter over guide-wire. CBD cannulation confirmed by aspiration or oozing of bile. Then endoscopic biliary sphincterotomy and endoscopic nasobiliary drainage or retrograde biliary drainage. 51 had biliary stents	Technical success: 81 without fluoroscopy. Complications in 8.1%:Biliary bleeding-2, acute cholecystitis-1, post-ERCP pancreatitis-2. All babies were healthy at up to 12 mo. follow-up. All babies had normal birth weights (> 3 kg). Mean Apgar score at 5 min = 9
Akcakaya A, 2009[69]	6 patients: mean gestational age = 23 wk, range: 14-34 wk	Choledocholithiasis-4, Cholangitis-1, Persistent biliary fistula after hydatid disease surgery-1 (undergoing 2 ERCPs)	All patients had biliary sphincterotomy and balloon sweeps. Precut sphincterotomy performed with needle-knife for 1 patient with impacted stone	Complete stone extraction confirmed by abdominal ultrasound. No post-ERCP complications, premature birth, abortion or intrauterine growth retardation were observed

Shelton J, 2008[68]	21 patients: first trimester-7, second trimester-9, third trimester-5	Jaundice and biliary colic-11, biliary pancreatitis-8, cholecystitis-1, abnormal intraoperative cholangiogram-1	Guide-wire inserted into CBD followed by sphincterotome over guide-wire. CBD cannulation then confirmed by suction of yellow bile *via* catheter in first 10 cases. In next 11 cases CBD cannulation confirmed by leakage of yellow bile around guide-wire. Then wire-guided biliary sphincterotomy performed followed by balloon sweeps to extract stones. Choledochoscopy used for bile duct clearance in 5 last cases	100% technical success without fluoroscopy. One case of moderate pancreatitis. All then became asymptomatic. Follow-up of 18 pregnancies: Uneventful delivery of healthy babies-17, premature delivery at 35 wk with low birth weight-1
Sharma SS, 2008[64]	11 patients: first trimester-2, second trimester-6, third trimester-3	Abdominal pain and jaundice-11, cholangitis-2, dilated CBD-11, gallstones-8	All had 2-stage procedures. First stage during pregnancy: biliary sphincterotomy and stenting without radiation, bile aspirated to confirm biliary cannulation. Second stage ERCP postpartum: Stents removed, cholangiogram performed. Stones removed by Dormia basket-8, mechanical lithotripsy-1, or open surgery-1, no residual stones-1	Marked symptomatic improvement after first stage of therapy. All had normal, full-term delivery. "Good" maternal and fetal outcomes

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; CBD: Common bile duct; MRCP: Magnetic resonance cholangiopancreatography.

retrospective design, and lack of comparative statistics[45]. Some studies focus on the technical success of the ERCP, without reporting fetal outcome altogether[64,65].

A recent trend is performing radiation-free ERCP (RFE) during pregnancy[34]. Transabdominal ultrasound has guided subsequent RFE, but this technique is cumbersome. In RFE a two-stage procedure may be performed, where the initial ERCP during pregnancy is temporizing, uses minimal or no fluoroscopy, and typically incorporates biliary sphincterotomy and stent placement; the subsequent postpartum ERCP is definitive[64,65]. In a patient presenting in late pregnancy, it is reasonable to perform a moderate sphincterotomy and insert a biliary stent to defer more definitive therapy to postpartum[64]. Performance of ERCP in the first trimester may involve risks of termination of pregnancy, especially if the ERCP is prolonged and entails considerable radiation exposure. Visualization of bile drainage after wire insertion or bile aspiration after catheter cannulation is currently usually used to confirm successful selective biliary cannulation. Shortcomings of this method include wires or catheters can inadvertently enter the cystic duct, chronically obstructed biliary systems may yield "white bile", and curled wires may cause bile duct injury that renders stent insertion difficult.

The initial case of RFE was inadvertent use of a needle-knife for an impacted common bile duct stone[66]. The first clinical series of RFE after ultrasound consisted of 6 pregnant women with acute pancreatitis or cholangitis[67]. The 6 patients underwent selective bile duct cannulation, biliary sphincterotomy, and successful gallstone removal, but two infants were born prematurely, including one with significant complications. Altogether 147 ERCP's have been performed during pregnancy without fluoroscopy in 8 clinical series, reflecting endoscopist ingenuity and technological progress (Table 4)[64,68-75]. These clinical data are extremely promising, with a very high rate of technical success (clearing of CBD stones), low rate of maternal complications, delivery of predominantly healthy babies, mostly normal birth weights, and typical delivery at term (Table 4)[64,68-75]. However, case series from tertiary academic centers may not be extrapolated to community hospitals. Radiation–free ERCP is ideal, but should not be pursued if this unduly prolongs the ERCP and increases the risks of complications, especially pancreatitis. Moreover, brief fluoroscopy with "ultra-short" (< 60 s) radiation exposure may produce as favorable fetal results as radiation-free ERCP.

EUS is now readily available and should be considered prior to RFE. EUS is especially useful to gauge CBD diameter; number, size, and morphology of gallstones; and may occasionally obviate the need for ERCP. Intraductal stone clearance can be demonstrated by a balloon pull-through. Intraductal ultrasound (IDUS) (Figure 1) is an underutilized modality to assess ductal clearance. Particularly expert endoscopists can perform trans-septal sphincterotomy; especially after inserting a low-profile stent into the presumptive pancreatic duct.

Choledochoscopy (cholangioscopy) is very useful to disrupt choledocholithiasis *via* laser therapy or lithotripsy and confirm ductal clearance[68,73,75]. It is less useful and potentially dangerous for selective duct cannulation because the 10 French insertion catheter is somewhat stiff and may not smoothly negotiate an angulated pancreatic duct. The procedure is selected according to the clinical scenario and physician expertise (Figure 2). ERCP is particularly challenging and potentially involves some risk during the first trimester.

Decisions regarding cholecystectomy in pregnant women with biliary disease is entwined with ERCP concerns. As aforementioned, the second trimester is usually the most favorable time for both ERCP and cholecystectomy. Cholecystectomy timing is determined by the patient's clinical course, with or without ERCP. Patients with

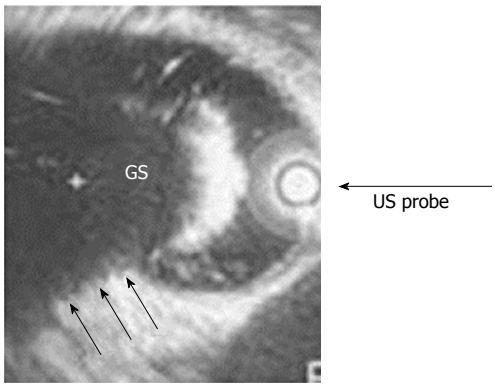

Figure 1 Intraductal ultrasound: Showing a gallstone in the common bile duct.

concomitant cholecystitis should undergo surgery as soon as feasible. A series of seven pregnant patients had good maternal and fetal outcomes after undergoing ERCP with biliary sphincterotomy, and stone extraction, followed by immediate cholecystectomy for biliary pancreatitis[76]. Delaying cholecystectomy may result in biliary complications later during pregnancy or postpartum[77,78].

A first trimester pregnant woman underwent concurrent laparoscopic cholecystectomy and ERCP *via* a rendezvous technique wherein a wire was inserted by the surgeon *via* the cystic duct, through the CBD, and into the small intestine; the endoscopist accessed this wire for cannulation at ERCP[79]. This combined procedure resulted in technical success and favorable fetal outcome. This combined method should minimize risks of pancreatitis, but requires prolonged operative time and extra anesthesia medications for the twin procedures. One endoscopist performed his own rendezvous technique *via* EUS after failed biliary cannulation during standard ERCP, with good results for the mother and the fetus[80].

Future prospects

Pancreatic ERCP during pregnancy may be reported in the future[81]. Magnetic technology currently applied to detect endoscope position during endoscopy (especially colonoscopy) may conceivably be applied to wires and catheters during ERCP[82]. A meta-analysis would be clinically beneficial; it would likely demonstrate comparable maternal and fetal outcomes with minimal radiation *vs* radiation-free ERCP. Clinical studies on efficacy of fetal heart rate monitoring during ERCP would be helpful. Data are sparse for ERCP during the first trimester. Long term follow-up data would be helpful on outcomes of children who received ERCP radiation in utero. Future technological improvements in ERCP may prove beneficial to the pregnant population.

A limitation of this review is that some of the data are from case reports which may be anecdotal and may be subject to reporting bias in that ERCP endoscopists may be more likely to report successful cases of ERCP during pregnancy. However, biases were minimized by systematically reviewing the literature. Errors in abstracting data from the literature were eliminated by two investigators independently reviewing all the analyzed publications. In conclusion, performance of ERCP during pregnancy is a substantial undertaking requiring endoscopist forethought, with potential use of multiple modalities including EUS. ERCP is generally safe during pregnancy. It should generally be avoided during the first trimester, and performed in the first trimester only for urgent and strong indications such as gallstone pancreatitis with documented choledocholithiasis, cholangitis, symptomatic choledocholithiasis, or jaundice. The endoscopist should frankly discuss procedural risks *vs* benefits with the patient. Radiation safety measures are paramount, as is the endoscopist's experience and technical skills. Various strategies and technologies may enhance biliary cannulation and ductal clearance during ERCP. Radiation–free ERCP is ideal, but should not unduly increase procedural time and risk of complications, especially pancreatitis.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is currently the standard technique for treating choledocholithiasis and associated complications, such as cholangitis, biliary pancreatitis, and biliary stricture, in the non-pregnant population. The approach in pregnant women with suspected choledocholithiasis, however, differs somewhat from that for non-pregnant patients because of concerns about the pregnant mother and the fetus, including procedure time, teratogenicity of intraprocedural medications, and fetal radiation exposure.

Research motivation

This work systematically collates the clinical data from the clinical studies, including the numerous small clinical series, to render these data accessible to clinicians. This work provides a systematic review of the rapidly evolving literature in this clinically booming field to provide highly important and clinically relevant updates on ERCP safety, efficacy, and recent technical improvements in pregnant patients.

Research objectives

This work reports numerous techniques to reduce radiation exposure and other safety precautions to decrease fetal risk from ERCP during pregnancy. Indeed, this work discusses in detail radiation free ERCP during pregnancy to completely eliminate teratogenic risks of radiation.

Research methods

This review encompassed more than 500 cases published in small clinical series and scattered reports, in addition to 58 cases recently reported in a retrospective Swedish registry study.

Research results

This work focuses on techniques to improve ERCP safety during pregnancy, including analysis of the relatively recently introduced radiation-free ERCP to completely eliminate the potential for radiation teratogenicity. Radiation-free ERCP is shown to be a relatively safe, and efficacious technique. However, more clinical data are required on this promising technique.

Research conclusions

This work shows that therapeutic ERCP is a reasonably safe therapy for the mother and the fetus during pregnancy, and it should be performed when indicated for symptomatic choledocholithiasis and its associated complications (including ascending cholangitis, gallstone pancreatitis, and biliary stricture)

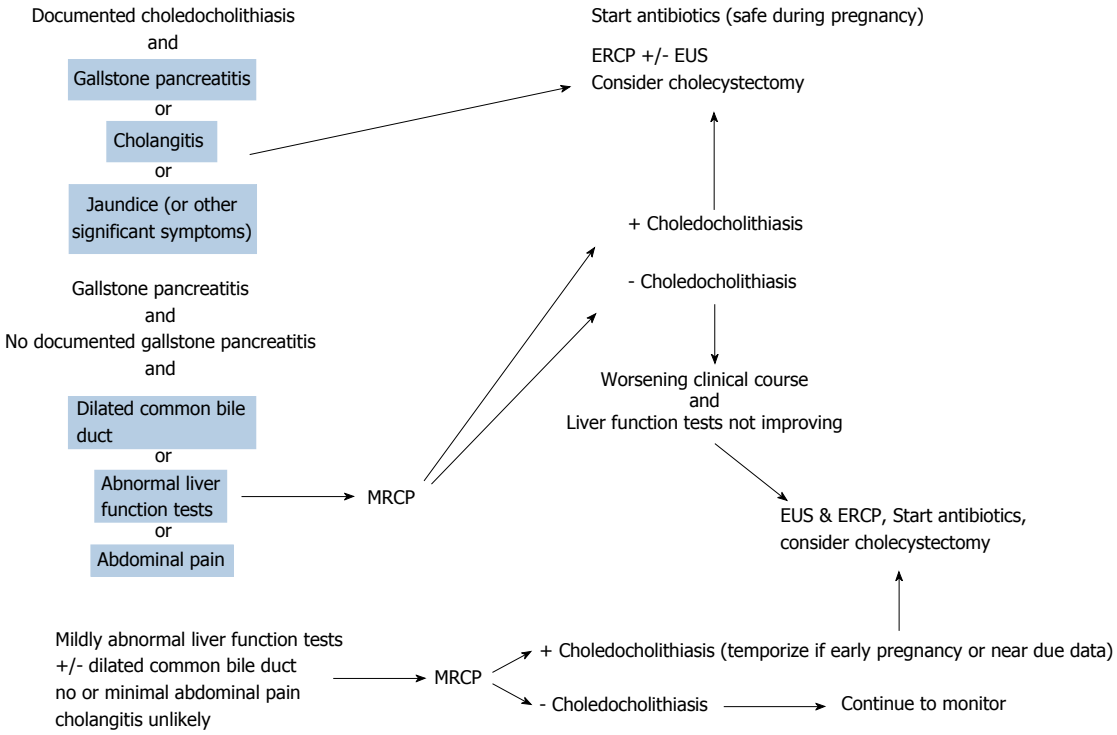

Figure 2 Approach to biliary disease during pregnancy. Patient diagnostic and treatment algorithm depending upon three different clinical presentations. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

during pregnancy. This work confirms that solely diagnostic ERCP should generally not be performed during pregnancy due to the risks of fetal radiation teratogenesis and induction of early labor, and should be replaced by diagnostic MRCP or endoscopic ultrasound. ERCP should not be performed during pregnancy for asymptomatic stones because of potential fetal risks; ERCPs can often be delayed to postpartum because patients have minimal clinical findings, or patients can directly undergo cholecystectomy during pregnancy without antecedent ERCP for acute cholecystitis.

Research perspectives

More data are needed on radiation-free ERCPs. This work describes technique modifications for therapeutic ERCP during pregnancy to improve procedural safety. It is hoped that clinicians adapt these technique modifications during ERCP to further improve ERCP safety and efficacy during pregnancy.

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P- Reviewer: Gkekas I, Khoury T, Sugimoto M, Wang ZY, Zhang QS
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