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MINIREVIEWS

Role of endoscopic ultrasound in vascular interventions: Where are we now?

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Abstract

From a mere diagnostic tool to an imperative treatment modality, endoscopic ultrasound (EUS) has evolved and revolutionized safer efficient options for vascular interventions. Currently it is an alternative treatment option in the management of gastrointestinal bleeding, primarily variceal type bleeding. Conventional treatment option prior to EUS incorporation had limited efficiency and high adverse events. The characterization and detail provided by EUS gives a cutting edge towards a holistically successful management choice. Data indicates that EUS-guided combination therapy of coil embolization and glue injection has the higher efficacy for the treatment of varices. Conversely, similar treatment options that exist for esophageal and other ectopic variceal bleeding was also outlined. In conclusion, many studies refer that a combination therapy of coil and glue injection under EUS guidance provides higher technical success with fewer recurrence and adverse events, making its adaptation in the guideline extremely favorable. Endo-hepatology is a novel disciple with a promising future outlook, we reviewed topics regarding portal vein access, pressure gradient measurement, and thrombus biopsy that are crucial interventions as alternative of radiological procedures. The purpose of this review is to provide an update on the latest available evidence in the literature regarding the role of EUS in vascular interventions. We reviewed the role of EUS in variceal bleeding in recent studies, especially gastric varices and novel approaches aimed at the portal vein.

Key Words: Endoscopic ultrasound; Cyanoacrylate; Coil injection; Gastric varices; Gastrointestinal bleeding; Vascular endoscopic treatments

Core Tip: Currently endoscopic ultrasound (EUS) is an alternative treatment option in the management of gastrointestinal bleeding, primarily variceal type bleeding. This manuscript tackles a comprehensive review for the uses of EUS in the majority of vascular interventions with regard to gastrointestinal bleeding and offers a directive for the technical aspects in carrying out a procedural treatment of combination coil and glue therapy for gastric varices.

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INTRODUCTION

The endoscopic ultrasound (EUS) technology has dramatically evolved since its conception in the 80s, transforming from a supplementary add-on of the diagnostic process to a core modality in the diagnosis and therapy in a wide range of diseases[1]. EUS diagnostic capability has evolved immensely in recent years primarily enhancing fine needle aspiration (FNA) and fine needle biopsy, the acquisition of particularly gastrointestinal (GI) and pancreato-biliary lesions, providing cytohistologic sampling[2]. Having the diagnostic sensitivity of 85% to 95% in detecting malignant pancreatic tumors and specificity of 100%, EUS guided FNA is being regarded as a main staple if not a gold standard by many experts[1]. Further extending the reach towards lesions of the pancreas, mediastinal adenopathy, GI tract submucosal lesions and retroperitoneal masses, EUS provides a detailed image and obtains tissue samples in a minimally invasive manner that is safe and accurate for diagnosis[3,4]. On the other hand, therapeutic EUS-guided drainage is a favored option in the management of pancreatic fluid collections, biliary and gallbladder diseases[5-7]. Moreover, the indications for interventional EUS grow more and more having nowadays a central role in the management of biliary diseases in altered anatomy, gastric outlet obstruction and post-surgical abdominopelvic fluid collection drainage[8-11].

Under the scope, focusing on various GI conditions, initially EUS provided clinicians with valuable information pertaining to clinical and anatomic information. Aspects such as the appearance, size and location of a structure indicated variable descriptive factors regarding a plethora of conditions[12]. Due to the proximity of the GI system to vascular structures, EUS today can provide precise interventions that target inaccessible, or less accessible surrounding vascular sites[12]. EUS has advanced as alternative treatment option in the management of GI bleeding providing an efficient treatment modality and offering fewer adverse events (AEs). Effective treatment options that are EUS guided exist, such as sclerotherapy, tissue adhesive injections, and coil embolization. Recently, the employment of glue injection and coil embolization techniques with EUS seem to be thriving in clinical practice. Stand-alone therapy options present with variable risk factors and complications, ultimately delegating to clinicians and technicians in the field to utilize a combination of both glue injection and coil embolization under the guidance of EUS[13]. The purpose of this review is to provide an update on the latest available evidence in the literature regarding the role of EUS in vascular interventions.

TECHNICAL FEATURES

Primarily, prior to the promotion of EUS, definitive understanding of the technical strengths and limitation it encompasses is key to its adoption into clinical practice. First and foremost, EUS provides precise targeting of vascular structure in direct proximity for the GI wall (Figure 1A). It further allows visualization reducing the risk of injection out of site[12]. It is also worth mentioning, the precision regarding biopsies of tissues is much higher than the conventional method. Furthermore, EUS provides a sort of 'check-up' following procedures such as the obliteration of a varix, that grants validity for a clinician achieving technical success. Conversely, nothing is without limitations and EUS is not short of either, ultrasonography remains to have a steep learning curve. Additionally, following the transmural access into deeper tissue, bleeding from the extra-luminal side is not accessible by endoscopy, causing

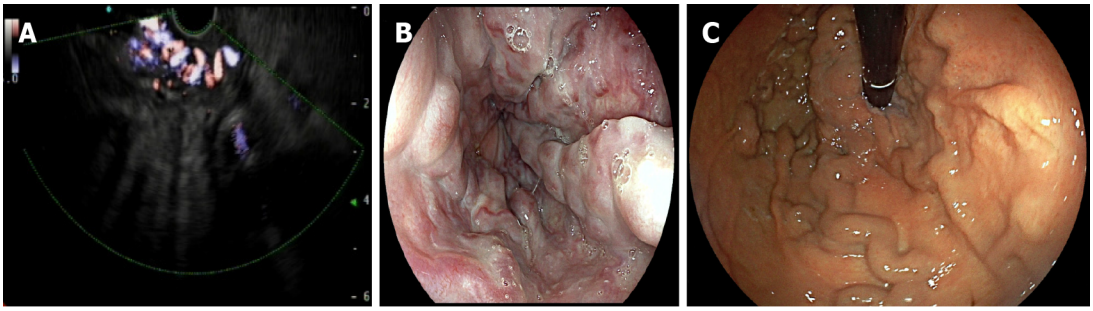

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Figure 1 Endoscopic images. A: Endoscopic ultrasound-Doppler detecting gastroesophageal varices; B: Endoscopic view of large esophageal varices (classified as grade 2 at Westaby classification)[19]; C: Endoscopic view in retroversion of gastro-esophageal varices (classified as gastroesophageal varix 2 at Sarin classification)[22].

urgent surgical or radiological therapy. Likewise, AEs exist with the use of EUS, although at a much lower rate than the conventional therapy, the risk still exists and may be fatal. The caliber of the EUS aspiration channel is restrictive and multiple predicaments arise[14]. Firstly, luminal contents may not be aspirated creating artifacts that hinder the sonographic image during the procedure. Secondly, the reduction in caliber size limits the apparatus from removing blood clots that not only obstruct the view but may lead to further thromboembolic events that may be fatal[15]. A larger range of accessories and devices designed for ultrasonography, miniature apparatus, correct antibiotic prophylaxis may tackles some of the limitations mentioned. Ultimately the standardization of a technique of injection, volume of injection, size of coils, and speed of injection are challenges to confront while adapting a universal methodology for any EUS-guided procedure[15].

Initially, a prior conventional endoscopic examination is necessary to confirm varix type and concomitant esophageal varices with gastric varices. The procedure should be performed with the patient under deep or conscious sedation, according to each institution protocol. Using a linear echoendoscope for the evaluation of varix size and treatment evaluation is the mode of choice[16]. Once the varix is identified under EUS, it is necessary to characterize the total diameter of the widest varix which should be punctured by a 19G needle[17]. It is important to choose the size of the coil depending on the size of the widest varix. More importantly, the size of the coil should not exceed the caliber of the vessel it is injected into. In case of glue injection, following the deployment of the coil, 2 mL of distilled water followed by 0.5 mL of N-butyl-2-cyanoacrylate, followed by another 2 mL of distilled water was injected and then the needle removed[17]. Lastly, EUS with Doppler flow is important for technical success evaluation. The presence or absence of flow within the varix is what is evaluated[6,16,17].

TYPE OF BLEEDING

Variceal bleeding

Variceal bleeding is known to be the most feared lethal complication of portal hypertension. Whilst gastric varices tend to be the most problematic; esophageal, rectal, and other ectopic locations present with serious complications. As described in further detail below, guidelines offer a wide range of therapeutic options depending on location of the varix, whether offering standard endoscopic, surgical, or interventional radiologic therapies, each come with strengths and weaknesses. While centering our focus on standard endoscopic treatments, we find major limitation in the addressed therapies, whether it's a matter of severe AEs and high risk or a high recurrence rate of the varix rebleeding and a low clinical outcome. Under EUS guidance, coincidentally due to higher precision of vascular targeting, the treatment options deemed more efficient with an overall higher success rate and clinical outcome[18]. Furthermore, the recommendation enclosed reports that EUS is a feasible safe option for patients who were unsuccessful candidates for conventional therapies[18].

Variceal classification

Different classifications for esophageal varices have been created, to mention a few: Dagradi, Conn's, Paquet's, Westaby, Calès and Soehendra[16]. The most used one are the Westaby and Dagradi's classification.

Westaby's offers a three-grade system classification of identifying the progression of esophageal varices classified as[19]: Grade 1 varices appearing as slight protrusion from the mucosa, which can be depressed with insufflation [20]; Grade 2 varices occluding less than 50% of the lumen (Figure 1B); Grade 3 varices occupying more than half of the lumen and are extremely close to one another with a confluent appearance.

Alternatively, the Dagradi classification is a five-grade system for esophageal varices classifieds as [20,21]: Grade 1 varices less than 2 mm in diameter that are linear or sigmoid in shape and appear with compression of the wall with the scope, they usually present as blue or red in color; Grade 2 are blue varices sized between 2-3 mm in diameter and are mildly tortuous or straight and elevated; Grade 3 are blue tortuous or straight varices sized between 3-4 mm in diameter; Grade 4 are varices larger than 4 mm that surround the esophageal lumen and are closely neighboring each other around the wall with or without mucosal cover; Grade 5 are grape like varices that occlude the lumen and present as red varies overlying blue varices; 'varices over varices.

Similarly, the most used classification for gastric varices is the 'Sarin's' classification[22]. Four different types based on their location in the stomach are classified as two types of gastroesophageal varix (GOV) and two types of isolated gastric varix (IGV)[23]. Type GOV1 are varices that extend in the cardia to lesser curvature of the stomach. Type GOV2 are varices that extend from the cardia towards the greater curvature of the stomach, terminating at the gastric fundus (Figure 1C). Type IGV1 are varices in the gastric fundus that do not extend to the esophagus. Type IGV2, also referred to as ectopic gastric varices occur in other parts of the stomach. To a certain degree many clinicians regard esophageal varices and type GOV1 as gastroesophageal varices whilst GOV2 and IGV1 are fundal varices[20,23].

ESOPHAGEAL VARICES

Esophageal variceal bleeding is much more common than gastric varices, with high morbidity and mortality but fortunately carries less detrimental complications. In essence esophageal varices is a collateral circulation that develops due to portal hypertension[13]. Esophageal varices hemodynamics differ from patient to another, thus making their treatment problematic[14]. Guidelines state that first line treatment of esophageal bleeding is to be treated by endoscopic band ligation followed by transjugular intrahepatic portosystemic shunt (TIPS) or endoscopic sclerotherapy, both pose significant risk to the patient[12]. Endoscopic preventative bleeding measures for esophageal varices include endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL)[18]. Primarily EIS, a much older technique, involved the embolization of the feeder veins by injecting a sclerosing agent that maintained the regression of the collateral circulation. Thus, by inhibiting the hemodynamics of the varices' the recurrence remained low[24]. Unfortunately, the complexity of delineating the circulations hemodynamics and the high complication risk associated, EIS remains a challenging option for the treatment of variceal esophageal bleeding. In efforts to a more effective treatment with less complications, EVL was developed[24]. EVL as the name suggests ligates the varices and thus blocks the flow of blood in the collateral area. Since the technique doesn't target the feeder vessel, recurrence rate is high. In hindsight EVL's main limitation is the lack of clinical and anatomical information on the hemodynamics of the circulation and the feeder vessel[25]. On the other hand, EUS provides a selective safe effective treatment option that can predict variceal recurrence, estimate the circulation's hemodynamics, and provide follow-up screening and management[26]. A study with the aim of studying the relationship of both treatments (EVL and EIS) recurrence used 3D-EUS and defined four main variceal circulation patterns as: cardial inflow without paraesophageal veins, cardial inflow with paraesophageal veins, azygos-perforating pattern, and a complex pattern. The study concluded the use of EVL to be limited to collaterals running parallel to the varices whilst sclerotherapy to be used for paraesophageal veins with a larger diameter and a perforation pattern[18]. Furthermore, the utilization of EUS technology provided effective directed treatment option of pattern types that aided a successful clinical outcome[27]. Moreover, in one study that utilized a sclerosing agent targeted under EUS guidance, an average of 2 to 3 sessions required to achieve complete obliteration. The study further reported in their cohort of 5 patients; no bleeding recurrence or death and one patient developed an esophageal stricture that was treated with balloon dilation[28].

GASTRIC VARICES

Standard therapy for gastric varices by current guidelines recommends the use of endoscopic cyanoacrylate (CYA)[29]. High bleeding rates and fatal AEs mandates the need for a more feasible option such as EUS guided. EUS-guided therapy provides high technical success and an overall better safety profile [24,29]. Romero-Castro *et al*[30] in a retrospective analysis that aimed at a direct comparison of the variable EUS-guided methods showed similar obliteration rated of gastric varices in both CYA injection and coil embolization (Table 1). Mohan *et al*[18] carried a meta-analysis that presented that the combination of EUS-coil/CYA had significantly fewer instances of gastric varices recurrence than EUS guided CYA injection (5.2% *vs* 15%). Furthermore, McCarty *et al*[31] reviewed a meta-analysis of 11 studies compared EUS-guided methods and discovered similar advantages to the combined approach. Their results showed that EUS-coil/CYA had a significantly higher rate of GV obliteration than either EUS-CYA (98% *vs* 96%) or EUS-coil (98% *vs* 90%). Moreover, the combination of EUS-coil/CYA had a

Table 1 Comparison of the main studies reporting data of endoscopic ultrasound guided treatments for gastric varices

Ref.	Study design	Number of patients	Technical success	Clinical success	Adverse events
Romero-Castro *et al*[30], 2013	Retrospective analysis of a prospectively maintained database	30 total patients, 11 ECA, 19 CYA	27/30 (90%)	18/19 (96.7%) CYA; 10/11 (90.9%) ECA	40% total AEs; CYA 11/19 (57.9%); ECA 1/11 (9.1%)
Lôbo *et al*[17], 2019	Randomized Controlled Trial	32 total patients; 16 ECA + CYA, 16 CYA	-	-	Early AEs: 8 (50%) ECA + CYA; 10 (62.5%) CYA. Pulmonary embolism: 4 (25%) ECA + CYA; 8 (50%) CYA
Robles-Medranda *et al* [29], 2019	Randomized Controlled Trial	60 total patients, 30 ECA + CYA; 30 ECA	60/60 (100%) in both groups	ECA + CYA 30/30 (100%), ECA 27/30 (90%)	ECA + CYA 2/30 (6.7%); ECA 1/30 (3.3%)
Bazarbashi *et al* [16], 2020	Prospective Study	40 total patients; 10 ECA, 30 CYA	10/10 (100%) ECA; 29/30 (96.7%) CYA	10/10 (100%) ECA; 26/30 (87%) CYA	10% ECA; 20% CYA

ECA: Endoscopic coil application; CYA: Cyanoacrylate; AE: Adverse event.

lower recurrence rate than their singular respective modalities. The combination modality had lower rebleeding rate and frequency of AE than EUS-CYA[29,32]. Data indicates that EUS-guided combination therapy of coil embolization and glue injection has the higher efficacy for the treatment of varices. Similarly, another interesting study reported that although combined therapy had a superior safety profile over EUS-guided CYA injection, when compared to EUS coil injection similar results were obtained[29]. However, an interesting notion to point out is that coil embolization is technically demanding when compared EUS- guided glue injection[14]. In efforts to reassess a proper direction for the leading choice of treatment, multiple factors come into play. Evaluating technical success, AEs, recurrence rate and clinical outcomes shape the best decision in moving forward[14].

A meta-analysis and systematic review that aimed to evaluate the effectiveness of the above-mentioned outcome measures, studied comparative groups of mono and combination modalities[31]. Overall technical success, clinical success, and AEs for EUS treatments was 100%, 97% and 14%, respectively. Moreover, EUSguided CYA + coil embolization resulted in a better technical and clinical success compared to CYA alone (100% *vs* 97% and 98% *vs* 96%) and coil embolization alone (99% *vs* 97% and 96% *vs* 90%)[18]. Similar results coming from a single center observational study outlines primary preventative prophylactic treatment of gastric varices and the use of combination EUS of coil and CYA glue injection as the preferred modality achieving 100% technical success, 96.7% gastric varices obliteration on EUS confirmation and post-treatment recurrence was at 2.5% and AEs at 4.9%[33].

EUS further provides an advantage in the use of CYA injection in the obliteration of gastric varices as an overall lower mean volume of the glue is needed to reach similar technical success with the same safety profile of rebleeding rates being (8.8% *vs* 23.7%)[32]. One study mentioned less incidence of pulmonary embolism for EUS guided coil embolization when compared to EUS CYA therapy[29]. Coil based therapy for the treatment of gastric varices was reported to be superior to traditional endoscopic therapy with CYA injection[16]. In another study, EUS guided coil therapy exhibited high technical success rates, low AE rates, superior time to rebleed, time to repeat transfusion, and time to repeat intervention when compared to endoscopic CYA injection[16]. The study further concluded that the rate of rebleeding in the CYA arm was 38% which was higher than what was that literature 20%-30%. A single center parallel RCT studied efficacy and safety of EUS-guided coil embolization and CYA injection *vs* EUS-guided coil embolization alone in the managing gastric varices. Interestingly, the immediate disappearance of varices was observed in 86.7% of patients treated with coils and CYA, *vs* 13.3% of patients treated with coils alone indicating the combination therapy to offer an immediate surveillance feature within the procedure. Likewise, the combined treatment, had 83.3% of patients free from reintervention when compared to coil alone 60%[34]. One study reported no statistical difference between EUS guided coils plus CYA *vs* conventional CYA technique in relation to the incidence of embolism. The study concluded a larger tendency of patients to develop embolism when compared to the conventional endoscopic technique without EUS[18]. With regards to the choice of tissue glue/adhesives, CYA, one study aims to evaluate the safety in applying EUS-guided modality of hydro coils in gastric varices. Hydro coils are coils coated with different types of expandable hydrogel polymers, causing rapid occlusion of vessels, and favoring thrombus formation. The study reported fewer recurrences 8.6% and no differences with regard to side effects when compared to CYA[31].

ECTOPIC VARICES

Following the recommendation of current guidelines, endoscopic band ligation and glue injection are

the established techniques for managing ectopic variceal bleeding[18]. One example are duodenal varices, common in end-stage patients with decompensated cirrhosis, current treatment options include TIPS, endoscopic band ligation or sclerotherapy. Commonly patients presenting with duodenal varices are referred to endoscopic treatment for bleeding prevention and EUS guided situates the clinicians technical outcome at an advantage[35]. EUS provides superior characterization of the variceal complex and offers higher obliteration with a lower recurrence rate in compared to the conventional treatments. Thus, offering a feasible safe option to manage these patients[14].

Rectal varices are a well-recognized complication of portal hypertension[36]. The perforator vein supplies the variceal circulation, which invaginates superficially and bleeds. Common treatment options include interventional radiology and surgery with a mortality rate documented as high as 80%[36]. Well regarded recommendation in a previous study showed that the injection 2 mL of N-butyl 2-CYA into the varix, thrombosed the collaterals and bleeding subsided in 2 wk[37]. In attempts to further reduce conventional interventional radiology mortality rates in the treatment of rectal varices, a study suggested the added benefit of EUS-guided treatment that provides an overall better diagnostic approach and higher technical success in targeting the perforator vein directly thus achieving homeostasis with less coils and hence overall less AE rates[36].

Additionally, most of the literature evaluating EUS guided techniques focus on upper GI bleeds. One study reported overall clinical outcome success in patients with rectal bleeding in all mono and combination modalities[37]. Authors recommend targeting the feeder vein in patients referred for endoscopic management if unfit for surgical or interventional radiological treatment[37]. Likewise, duodenal ectopic varices usually present in patients with end-stage liver disease, which are referred for endoscopic treatment to prevent bleeding. In one study authors recommended EUS-guided interventions, specifically combined therapy as it offers a superior complete obliteration rate to monotherapy[35].

Non-variceal bleeding

Upper GI bleeding not attributed to varices is common having multiple etiologies, peptic ulcer disease, erosive diseases, Mallory-weiss syndrome, Dieulafoy's lesions, gastric antral vascular ectasia, peripancreatic pseudoaneurysm and others (Figure 2). Definitive management measures involving EUS-guided therapies provide a novel treatment option with optimal efficacy. As a result of the steep learning curve and the need of extensive training programs in endosonography, EUS-guided angiotherapy for acute GI bleeding is limited to tertiary centers. EUS-guided management of non-variceal upper GI bleeding is an innovative option especially in cases of recurrence. Simultaneous characterization of the bleed and intra-procedural ensuring of therapy effectiveness provides an extra edge in comparison to conventional therapy[15]. That being said, literature on the matter is limited and no randomized controlled trials are available. Further studies need to clarify efficacy and safety in larger robust trials.

PSEUDOANEURYSM EMBOLIZATION

Pseudoaneurysms are blood collections that surround injured tissue, commonly known as false aneurysms and differ from true aneurysms, which form a blood-filled sac and bulge from the vessel wall[38]. With a prevalence of 0.04-0.1%, pseudoaneurysms are commonly associated with the splenic artery. Importantly, pseudoaneurysms usually occur following abdominal infections or post-pancreatitis[39]. Pseudoaneurysms are asymptomatic in most cases and usually appear as an incidental finding on radiological graphs. Due to the detrimental high rupture risks of up to 20%, allow for EUS-guided therapy to be an effective option for patients[40]. Many case-reports and series outlined good outcomes with obliteration of pseudoaneurysm following EUS-guided treatment, as reported by Mann *et al*[27], in a recent review of the literature. Recently, one study by Rai *et al*[41], aimed to study EUS-guided glue and coil injection in six patients who failed angiographic embolization of splenic artery pseudoaneurysm. Complete obliteration was achieved in all patients with larger aneurysms, requiring a 'larger' injection of coils and glue (1-2 mL). Moreover, no AEs occurred in any of these patients. Looking forward, this may provide an effective technique for the treatment of pseudoaneurysm in different abdominal segment accessible under EUS-guidance. Table 2 outline technical features from case report series on therapeutic management of pseudoaneurysms under EUS-guidance.

ENDO-HEPATOLOGICAL INTERVENTIONS

Nearing the last decade, a sub discipline of endoscopy named "Endo-hepatology", was introduced. In an aim to move towards a more accurate diagnosis, former procedures such as diagnostic biopsies and pressure measurements were advanced. Body habitus always posed as a challenging limitation whilst performing a biopsy of the liver however, using EUS, circumventing this problem became feasible and furthermore, simultaneous bi-lobar biopsies were possible[42]. EUS also improved patients' perception

Table 2 Case reports on endoscopic ultrasound-guided treatment of pseudoaneurysms

Ref.	Design	Technical success (%)	Adverse events	Recurrence	Needle size	Treatment
Robb *et al*[61], 2012	Case Report	100	None	None after 5 mo follow-up	19G	Psuedoaneurysm embolization
Gamanagatti *et al* [62], 2015	Case Report	100	None	Recurrence; asymptomatic	22G	Thrombin injection 300-500 units
Mann *et al*[27], 2017	Case Report	100	Not reported	None after 2 wk follow-up	19G	5 coils of 10 mm size were placed, 3000 units of thrombin injected
Jhajharia *et al*[63], 2018	Case Report	100	Not reported	None in all three patients	Not reported	1000 units of thrombin
Gunjan *et al*[63], 2018	Case Report	100	Not reported	None after 9 mo follow-up	19G	3 mL of undiluted N-butyl-cyanoacrylate
Sharma *et al*[65], 2019	Case Report	100	None	Full obliteration on 2-wk follow-up	19G	Five 10 mm coils placed, 6 mL of 3000 units of thrombin injected in six boluses of 500 units each

G: Gauge.

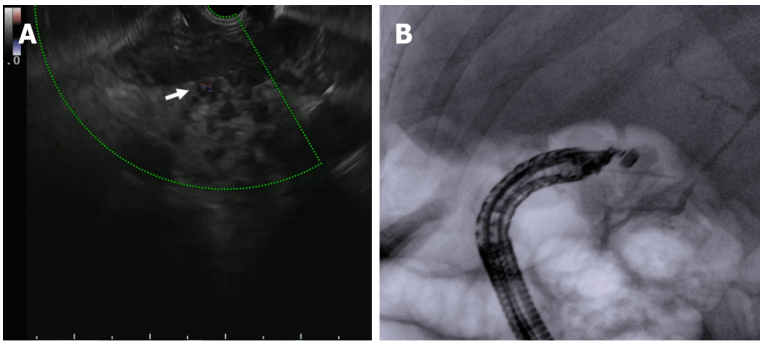

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Figure 2 Embolization of the gastroduodenal artery with cyanoacrylate glue due to active bleeding. A: Ultrasound view of the gastroduodenal artery (arrow); B: Fluoroscopic view of the gastroduodenal artery.

of undergoing a biopsy, due to the decreased recovery time and better tolerance overall. The added benefit did not revolve around technical expertise, as previous options required less technical training. The advantage lies with the reduction in sampling error due to the bi-lobar biopsies[42]. Additionally, EUS biopsies can be concurrently carried out with portal pressure measurements in a singular procedure, providing a more appealing option to patients than the trans-jugular approach. That anatomic proximity of the stomach and duodenum to major vascular structures, make EUS a vital technique in accessing structures such as the portal vein (PV). Existing applications of PV interventions using EUS include sampling, embolization, thrombolysis, and stent placement[27].

PV interventions: Sampling, pressure measurement and embolization

Circulating tumor cells (CTC) in the PV offer a positive predictive value of liver metastasis from pancreatic and colorectal cancers. The sampling of CTC under EUS guided access is vital, as CTC are more prevalent in the PV than in the peripheral blood. This provides an advantage with EUS, in order to sample tumor cells for further analysis[43]. The first report of EUS-guided PV sampling was in 2015, followed by another study in 2017 that similarly reported the safety and technical feasibility of the technique[43]. Chapman and Waxman[44] studied the propensity of CTCs as compared to sampling the PV under EUS guidance (19 gauge) with peripheral blood. In 18 patients, 100% sampling of CTC from the PV was achieved in comparison to 22.2% from the peripheral blood. Methodologically, the literature suggests multiple levels of consideration for PV sampling under EUS-guidance, due to limited data on safety and insubstantial unanimity of the technical feature of the procedure. Primarily, all bleeding risk should be addressed prior to the procedure and monitored anesthesia is an advocated preference in many studies. Secondarily, pre-assessing the PV under ultrasonography and FNA vein sampling was reviewed. The EUS-FNA needles available in today's market are the 19, 22, and 25 gauge sizes[44]. Chapman and Waxman[43], recommended the use of a 19-gauge FNA needle to allow adequate blood flow, that minimizes the time within the vessel to decreases clotting as compared to the smaller needles.

Ultimately, there is a lack of studies that assess the viability of the specimens obtained and the feasibility of the methodology. It is crucial to assess the patency of the vasculature with ultrasonographic doppler prior to the FNA access, in order to better reduce AEs.

Portal pressure gradient is an important measurement for the diagnosis of portal hypertension. Regardless of clinical evidence, a hepatic venous pressure gradient of 10 mmHg or more defines the presence of portal hypertension and is an important indicator of PH complication, most often for cirrhosis. Currently, a percutaneous approach exists for measuring PV pressure through a trans jugular access to the PV *via* the hepatic veins. Reduced conformity from patients due to catheterization makes an EUS-guided option more favorable[45].

Following the development of the compact manometer, EUS-guided portal pressure gradient measurement with a needle in the PV and manometer, accurately reflect an indicator of liver disease [27]. Under EUS, a 22-gauge FNA needle connected to a compact manometer, accurate hepatic venous pressure gradient measurement can be attained[46]. In a recent study by Hajifathalian *et al*[47], a simultaneous EUS-guided portosystemic pressure measurement and liver biopsy sampling in 24 patients with suspected liver disease or cirrhosis, was performed. Twenty-three patients reached technical success (96%) for portosystemic gradient measurement and 100% technical success for liver biopsy. The study concluded that EUS portosystemic gradient measurement and liver biopsy sampling provided a safe and feasible option in clinical practice. Table 3 lists studies on PV pressure gradient measurement, outlining technical success, features and complications, adapted from[48].

In the management of liver diseases, PV embolization (PVE) n is a possible intervention aimed at inducing atrophy of a lobe of the liver. This is advantageous, as it reduces the volume of the injured lobe prior to resection and concomitantly hypertrophies other healthy lobes, to decrease hepatic dysfunction and aiding preoperative preparations to liver lobectomy[27]. PVE is limited in multiple studies to animal models, due to the high-risk association with AEs, such as liver dysfunction. Loffroy *et al*[49] outlined PVE technique by accessing the portal system under EUS. Puncturing the peripheral branch by way of puncturing the left and embolizing the right branch is advantageous over puncturing and embolizing the right branch, due to easier catheterization. This method is conversely disadvantageous due to a high risk of damaging healthy liver remnants. Cirrhotic patients with portal pressure gradient larger than 12 mmHg, should avoid PVE due to detrimental AEs. Regarding the choice of the embolic agent, the authors suggested the use of a mixture of n-butyl-cyanoacrylate and iodized oil due to its rates of low morbidity. In anticipation to future advances, PVE under EUS-guidance can be appealing intervention in managing patients prior to surgical lobectomy.

Angiography

The direct access to the PV during an angiography may provide valuable clinical information. Unfortunately, routine practice avoids its implementation due to its invasive nature and high risk of complications[50]. A preliminary study in this field highlighted this fact in greater detail, as it showed that puncturing the PV with a 22-gauge needle led to high-risk bleeding measures in a porcine model[51]. In one study that evaluated the feasibility and safety of EUS-guided PV angiography with a smaller-caliber (25 gauge) FNA needle using carbon dioxide (CO_2) as a contrast agent in a porcine model. In 6 animal experimental trials, the authors achieved (19.83 ± 1.68 s) opacification of the entire portal system (visualization score 4.33 ± 0.52). The study reported no complications intraoperatively or at post-mortem examination, concluding that the study was feasible, safe, and technically simple. It is imperative to note that a major limitation to such studies is that they are acute animal models[52]. Replication into human disease remains confined in a plethora of possible complications and high bleeding risk.

Thrombus FNA

A large majority of patients suffering from hepatocellular carcinoma (HCC), have PV thrombosis. PV tumor thrombosis (PVTT) is essential as it is a poor prognostic sign and a contraindication for surgical hepatic resection. Extrahepatic PV access under EUS guidance, manages to access the thrombus without puncturing liver parenchyma, a favorable option for patients[27]. In 2015, Kayar *et al*[53] presented a case series of three cases that failed the normal route of imaging diagnosis of PV thrombus. Alternatively, from prior case reports, the patients were diagnosed with EUS-FNA of the PV thrombus as a first line diagnostic option. In all three cases presented, the authors used a 25-gauge FNA needle to biopsy the thrombus. Table 4 reports recent studies that highlighted cases of thrombus FNA-biopsy under EUS, notably when failed radiological diagnosis was unable to accurately stage HCC. Interestingly, Gimeno Garcia *et al*[54] in a multicentral study found that post EUS-FNA of thrombus, upstaging of HCC was prevalent up to 85.70%. In accordance with this finding, EUS-FNA biopsy of PVTT provides the most accurate staging diagnosis of HCC. High prospects for an EUS-guided intervention in diagnosing PVTT in patients that failed prior routes exist and should be studied in large RCT for a more widespread adaptation in everyday practice.

Drug administration

Even since the conception of curvilinear array echoendoscope in the 90's, the possibility to access structures with a needle under ultrasonographic visualization made treatment options to inaccessible

Table 3 Table summarizing technical features, success, and complications of studies on portal vein pressure gradient measurement

Ref.	Design	Technical success (%)	Adverse events	Post-procedural necropsy	Gauge needle used
Lai *et al*[51], 2004	Comparative Study - Animal Model	90	Subserosal hematoma in one porcine subject	After 4 d	22
Giday *et al*[52], 2007	Comparative Study - Animal Model	100	None	Day 0 and after 2 wk	19
Buscaglia *et al*[66], 2008	Comparative Study - Animal Model	100	None	Postprocedural	19
Huang *et al*[67], 2016	Comparative Study - Animal Model	100	None	Not reported	25
Schulman *et al*[68], 2016	Comparative Study - Animal Model	100	None	Postprocedural	25
Garg and Rustagi [48], 2017	Human Pilot Study	100	None	Not reported	25
Garg and Rustagi [48], 2017	Human Pilot Study	100	None	Occured on day 0, 1 and 7	25
Huang *et al*[69], 2017	Human Pilot Study	100	None	Not reported	25
Zhang *et al*[46], 2021	Prospective Study	91.70	None	Not reported	22

Table 4 Table summarizing studies and case reports of portal vein thrombus biopsy

Ref.	Design	Technical success (%)	Adverse events	Upstaging post EUS-FNA	Cytological analysis
Gimeno Garcia *et al* [54], 2018	Multicenter Study	87.50	None	85.70%	Used to determine final diagnosis
Rustagi *et al*[70], 2017	Prospective Study	100	None	37.50%	Malignant cytology in 12 patients out of 17 (70.6%; 10 positive, 2 suspicious)
Kayar *et al*[53], 2015	Case Report	100	None	Not reported	Invasion of PV by HCC
Moreno *et al*[71], 2014	Case Report	100	None	Not reported	Invasion of PV by HCC
Michael *et al*[72], 2011	Case Report	100	None	Not reported	Malignant cells consistent with poorly differentiated HCC

HCC: Hepatocellular carcinoma; EUS: Endoscopic ultrasound; PV: Portal vein; FNA: Fine needle aspiration.

structures possible. Further evolving into a therapeutic tool, being a minimally invasive approach for treating benign lesions, relieving compartmental pain, and controlling growth in unresectable malignancies is cutting edge[55]. EUS-guided therapeutic administration has been implemented apart from its varying levels of efficacy[56]. These ablative therapies under EUS-guidance are not a sole alternative to surgical resection, especially for metastatic tumors, but represent an option for patients that are not eligible for surgery. Moreover, recent studies show that chemotherapeutic administration into the PV increases the drug concentration in hepatic tissue than its systemic counterpart[57]. In 2016, an EUS-guided intervention for the injection of the PV was studied in a porcine model. Using a 22-gauge needle, 100mg of irinotecan, albumin-bound paclitaxel nanoparticles and doxorubicin loaded microbeads were injected into the PV. The study reported technical success in all animals, with no acute AEs occurring, suggesting a possible future avenue to be explored in human diseases[58].

CONCLUSION

Regrettably, to the best of our knowledge, EUS-guided treatment still has limitations and further studies are needed to demonstrate superiority over conventional medical and radiological therapies[18]. Primarily the steep learning curve and the need for expertise that may not be dispersed in all centers make it extremely difficult for guidelines to adapt strict recommendations in clinical practice[59]. Moreover, due to this revolutionary technology still being in the premature stages of adaptation into

clinical practice, a unified or standardized methodology doesn't exist. Whether the type of echo-endoscope, the positioning during therapy or the type of equipment used, a non-universal approach makes room for variable clinical outcomes and technical success rates[60]. On the other hand, EUS-guided therapy has potential to improve and become a main staple in the management of gastric varices [32]. In conclusion, EUS is without a doubt a novel diagnostic and therapeutic option for a variety of vascular complications, principally at the moment gastric variceal hemorrhage[59]. EUS offers a better understanding of the anatomic and hemodynamic components associated with the variceal system and offers advanced therapeutic options with sounder clinical outcomes. Although limited to major tertiary centers and operator dependence with a long learning curve, the adoption of EUS into clinical practice is plausible if EUS procedures were standardized, enhanced training tools for clinicians and better universal image interpretation methodology[26]. Artificial intelligence in aiding clinical technicians with image interpretation may be a captivating step in the right direction in the evolution of this vital technology.

FOOTNOTES

Author contributions: Fugazza A and Khalaf K conceived the design of the work, writing the article and acquiring data; Colombo M, Carrara S, Spadaccini M, Koleth G, Troncone E and Maselli R acquired data and prepared the figures; Repici A and Anderloni A revised it critically for important intellectual content; all authors reviewed and approved the final version of the paper.

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REFERENCES

1 **Simons-Linares CR**, Chahal P. Advances in Interventional Endoscopic Ultrasound (EUS): A Technical Review. *J Clin Gastroenterol* 2020; **54**: 579-590 [PMID: 32301834 DOI: 10.1097/MCG.0000000000001337]
2 **Di Leo M**, Crinò SF, Bernardoni L, Rahal D, Auriemma F, Correale L, Donato G, Massidda M, Anderloni A, Manfrin E, Armellini E, Poliani L, Fugazza A, Semeraro R, Occhipinti P, Repici A, Carrara S. EUS-guided core biopsies of pancreatic solid masses using a new fork-tip needle: A multicenter prospective study. *Dig Liver Dis* 2019; **51**: 1275-1280 [PMID: 31010744 DOI: 10.1016/j.dld.2019.03.025]
3 **Fugazza A**, Bizzarri B, Gaiani F, Manfredi M, Ghiselli A, Crafa P, Carra MC, de'Angelis N, de'Angelis GL. The role of endoscopic ultrasound in children with Pancreatobiliary and gastrointestinal disorders: a single center series and review of the literature. *BMC Pediatr* 2017; **17**: 203 [PMID: 29212476 DOI: 10.1186/s12887-017-0956-z]
4 **Tamanini G**, Cominardi A, Brighi N, Fusaroli P, Lisotti A. Endoscopic ultrasound assessment and tissue acquisition of mediastinal and abdominal lymph nodes. *World J Gastrointest Oncol* 2021; **13**: 1475-1491 [PMID: 34721779 DOI: 10.4251/wjgo.v13.i10.1475]
5 **Parsa N**, Nieto JM, Powers P, Mitsuhashi S, Abdelqader A, Hadzinakos G, Anderloni AA, Fugazza A, James TW, Arlt A, Ellrichmann M, Aparicio JR, Trindade AJ, Stevens TK, Chahal P, Shah SL, Messallam AA, Lang G, Fejleh MP, Benias PC, Sejpal DV, Jones J, Mir FF, Aghaie Meybodi M, Ichkhanian Y, Vosoughi K, Novikov AA, Irani SS, Pawa R, Ahmed AM, Sedarat A, Hsueh W, Hampe J, Sharaiha RZ, Berzin TM, Willingham FF, Kushnir VM, Brewer Gutierrez OI, Ngamruengphong S, Huggett MT, Baron TH, Repici A, Adler DG, Nasr JT, Kowalski TE, Kumbhari V, Singh VK, Khashab MA. Endoscopic ultrasound-guided drainage of pancreatic walled-off necrosis using 20-mm *vs* 15-mm lumen-apposing metal stents: an international, multicenter, case-matched study. *Endoscopy* 2020; **52**: 211-219 [PMID: 32000275 DOI: 10.1055/a-1096-3299]

6 **Fugazza A**, Colombo M, Repici A, Anderloni A. Endoscopic Ultrasound-Guided Gallbladder Drainage: Current Perspectives. *Clin Exp Gastroenterol* 2020; **13**: 193-201 [PMID: 32523368 DOI: 10.2147/CEG.S203626]

7 **Fugazza A**, Fabbri C, Di Mitri R, Petrone MC, Colombo M, Cugia L, Amato A, Forti E, Binda C, Maida M, Sinagra E, Repici A, Tarantino I, Anderloni A; i-EUS Group. EUS-guided choledochoduodenostomy for malignant distal biliary obstruction after failed ERCP: a retrospective nationwide analysis. *Gastrointest Endosc* 2022; **95**: 896-904.e1 [PMID: 34995640 DOI: 10.1016/j.gie.2021.12.032]

8 **Troncone E**, Fugazza A, Cappello A, Del Vecchio Blanco G, Monteleone G, Repici A, Teoh AYB, Anderloni A. Malignant gastric outlet obstruction: Which is the best therapeutic option? *World J Gastroenterol* 2020; **26**: 1847-1860 [PMID: 32390697 DOI: 10.3748/wjg.v26.i16.1847]

9 **Mudireddy PR**, Sethi A, Siddiqui AA, Adler DG, Nieto J, Khara H, Trindade A, Ho S, Benias PC, Draganov PV, Yang D, Mok S, Confer B, Diehl DL. EUS-guided drainage of postsurgical fluid collections using lumen-apposing metal stents: a multicenter study. *Gastrointest Endosc* 2018; **87**: 1256-1262 [PMID: 28843581 DOI: 10.1016/j.gie.2017.08.011]

10 **Tanisaka Y**, Mizuide M, Fujita A, Ogawa T, Suzuki M, Katsuda H, Saito Y, Miyaguchi K, Tashima T, Mashimo Y, Ryozawa S. Recent Advances of Interventional Endoscopic Retrograde Cholangiopancreatography and Endoscopic Ultrasound for Patients with Surgically Altered Anatomy. *J Clin Med* 2021; **10** [PMID: 33921247 DOI: 10.3390/jcm10081624]

11 **Fugazza A**, Anderloni A, Paduano D, Badalamenti M, Maselli R, Carrara S, Gabbiadini R, Colombo M, Spadaccini M, Cappello A, Haber G, Repici A. Underwater cap-assisted endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy: a pilot study. *Endoscopy* 2021; **53**: 927-931 [PMID: 33197940 DOI: 10.1055/a-1311-9779]

12 **Anastasiou J**, Berzin TM. Endoscopic Ultrasound-Guided Vascular Interventions: From Diagnosis to Treatment. *Saudi J Med Med Sci* 2018; **6**: 61-67 [PMID: 30787823 DOI: 10.4103/sjmms.sjmms_131_17]

13 **Pavic T**, Mikolasevic I, Kralj D, Blazevic N, Skrtic A, Budimir I, Lerotic I, Hrabar D. Role of Endoscopic Ultrasound in Liver Disease: Where Do We Stand? *Diagnostics (Basel)* 2021; **11** [PMID: 34829368 DOI: 10.3390/diagnostics11112021]

14 **Fujii-Lau LL**, Law R, Wong Kee Song LM, Gostout CJ, Kamath PS, Levy MJ. Endoscopic ultrasound (EUS)-guided coil injection therapy of esophagogastric and ectopic varices. *Surg Endosc* 2016; **30**: 1396-1404 [PMID: 26139494 DOI: 10.1007/s00464-015-4342-3]

15 **De Angelis CG**, Cortegoso Valdivia P, Rizza S, Venezia L, Rizzi F, Gesualdo M, Saracco GM, Pellicano R. Endoscopic Ultrasound-Guided Treatments for Non-Variceal Upper GI Bleeding: A Review of the Literature. *J Clin Med* 2020; **9** [PMID: 32245209 DOI: 10.3390/jcm9030866]

16 **Bazarbashi AN**, Wang TJ, Jirapinyo P, Thompson CC, Ryou M. Endoscopic Ultrasound-Guided Coil Embolization With Absorbable Gelatin Sponge Appears Superior to Traditional Cyanoacrylate Injection for the Treatment of Gastric Varices. *Clin Transl Gastroenterol* 2020; **11**: e00175 [PMID: 32677809 DOI: 10.14309/ctg.0000000000000175]

17 **Lôbo MRA**, Chaves DM, DE Moura DTH, Ribeiro IB, Ikari E, DE Moura EGH. Safety and efficacy of EUS-guided coil plus cyanoacrylate versus conventional cyanoacrylate technique in the treatment of gastric varices: a randomized controlled trial. *Arq Gastroenterol* 2019; **56**: 99-105 [PMID: 31141079 DOI: 10.1590/S0004-2803.201900000-08]

18 **Mohan BP**, Chandan S, Khan SR, Kassab LL, Trakroo S, Ponnada S, Asokkumar R, Adler DG. Efficacy and safety of endoscopic ultrasound-guided therapy *vs* direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis. *Endoscopy* 2020; **52**: 259-267 [PMID: 32028533 DOI: 10.1055/a-1098-1817]

19 **Westaby D**, Macdougall BR, Melia W, Theodossi A, Williams R. A prospective randomized study of two sclerotherapy techniques for esophageal varices. *Hepatology* 1983; **3**: 681-684 [PMID: 6352448 DOI: 10.1002/hep.1840030509]

20 **Abby Philips C**, Sahney A. Oesophageal and gastric varices: historical aspects, classification and grading: everything in one place. *Gastroenterol Rep (Oxf)* 2016; **4**: 186-195 [PMID: 27324725 DOI: 10.1093/gastro/gow018]

21 **Dagradi AE**, Stempien SJ, Owens LK. Bleeding esophagogastric varices. An endoscopic study of 50 cases. *Arch Surg* 1966; **92**: 944-947 [PMID: 5295832 DOI: 10.1001/archsurg.1966.01320240132029]

22 **Sarin SK**, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992; **16**: 1343-1349 [PMID: 1446890 DOI: 10.1002/hep.1840160607]

23 **Jakab SS**, Garcia-Tsao G. Evaluation and Management of Esophageal and Gastric Varices in Patients with Cirrhosis. *Clin Liver Dis* 2020; **24**: 335-350 [PMID: 32620275 DOI: 10.1016/j.cld.2020.04.011]

24 **Al-Khazraji A**, Curry MP. The current knowledge about the therapeutic use of endoscopic sclerotherapy and endoscopic tissue adhesives in variceal bleeding. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 893-897 [PMID: 31389265 DOI: 10.1080/17474124.2019.1652092]

25 **Van Stiegmann G**, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. *Gastrointest Endosc* 1988; **34**: 113-117 [PMID: 3259195 DOI: 10.1016/s0016-5107(88)71274-2]

26 **Nagashima K**, Irisawa A, Tominaga K, Kashima K, Kunogi Y, Minaguchi T, Izawa N, Yamamiya A, Yamabe A, Hoshi K, Goda K, Iijima M. The Role of Endoscopic Ultrasound for Esophageal Varices. *Diagnostics (Basel)* 2020; **10** [PMID: 33255736 DOI: 10.3390/diagnostics10121007]

27 **Mann R**, Goyal H, Perisetti A, Chandan S, Inamdar S, Tharian B. Endoscopic ultrasound-guided vascular interventions: Current insights and emerging techniques. *World J Gastroenterol* 2021; **27**: 6874-6887 [PMID: 34790012 DOI: 10.3748/wjg.v27.i40.6874]

28 **Lahoti S**, Catalano MF, Alcocer E, Hogan WJ, Geenen JE. Obliteration of esophageal varices using EUS-guided sclerotherapy with color Doppler. *Gastrointest Endosc* 2000; **51**: 331-333 [PMID: 10699783 DOI: 10.1016/s0016-5107(00)70363-4]

29 **Robles-Medranda C**, Oleas R, Del Valle R, Binmoeller KF. EUS-guided therapy of gastric varices (with video). *Endosc Ultrasound* 2020; **9**: 280-283 [PMID: 32913153 DOI: 10.4103/eus.eus_55_20]

30 **Romero-Castro R**, Ellrichmann M, Ortiz-Moyano C, Subtil-Inigo JC, Junquera-Florez F, Gornals JB, Repiso-Ortega A, Vila-Costas J, Marcos-Sanchez F, Muñoz-Navas M, Romero-Gomez M, Brullet-Benedi E, Romero-Vazquez J, Caunedo-Alvarez A, Pellicer-Bautista F, Herrerias-Gutierrez JM, Fritscher-Ravens A. EUS-guided coil *vs* cyanoacrylate therapy for the treatment of gastric varices: a multicenter study (with videos). *Gastrointest Endosc* 2013; **78**: 711-721 [PMID:

23891417 DOI: 10.1016/j.gie.2013.05.009]
31 **McCarty TR**, Bazarbashi AN, Hathorn KE, Thompson CC, Ryou M. Combination therapy *versus* monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis. *Endosc Ultrasound* 2020; **9**: 6-15 [PMID: 31417066 DOI: 10.4103/eus.eus_37_19]
32 **Thiruvengadam SS**, Sedarat A. The Role of Endoscopic Ultrasound (EUS) in the Management of Gastric Varices. *Curr Gastroenterol Rep* 2021; **23**: 1 [PMID: 33389241 DOI: 10.1007/s11894-020-00801-2]
33 **Kouanda A**, Binmoeller K, Hamerski C, Nett A, Bernabe J, Shah J, Bhat Y, Watson R. Safety and efficacy of EUS-guided coil and glue injection for the primary prophylaxis of gastric variceal hemorrhage. *Gastrointest Endosc* 2021; **94**: 291-296 [PMID: 33539908 DOI: 10.1016/j.gie.2021.01.025]
34 **Robles-Medranda C**, Oleas R, Valero M, Puga-Tejada M, Baquerizo-Burgos J, Ospina J, Pitanga-Lukashok H. Endoscopic ultrasonography-guided deployment of embolization coils and cyanoacrylate injection in gastric varices *vs* coiling alone: a randomized trial. *Endoscopy* 2020; **52**: 268-275 [PMID: 32126576 DOI: 10.1055/a-1123-9054]
35 **Bahdi F**, George R, Patel K. EUS-guided coiling and cyanoacrylate injection of ectopic duodenal varices. *VideoGIE* 2021; **6**: 35-37 [PMID: 33490754 DOI: 10.1016/j.vgie.2020.09.007]
36 **Bazarbashi AN**, Thompson CC, Ryou M. Targeting the perforator vein: EUS-guided coil embolization for the treatment of bleeding rectal varices. *VideoGIE* 2020; **5**: 434-436 [PMID: 32954109 DOI: 10.1016/j.vgie.2020.05.008]
37 **Rana SS**, Sharma R, Gupta R. Refractory rectal variceal bleeding treated with EUS-guided coil embolization. *Endosc Ultrasound* 2021; **10**: 141-142 [PMID: 33353904 DOI: 10.4103/eus.eus_63_20]
38 **Rivera PA**, Dattilo JB. Pseudoaneurysm. Treasure Island (FL): StatPearls Publishing, 2022
39 **Berceli SA**. Hepatic and splenic artery aneurysms. *Semin Vasc Surg* 2005; **18**: 196-201 [PMID: 16360576 DOI: 10.1053/j.semvascsurg.2005.09.005]
40 **Cordova AC**, Sumpio BE. Visceral Artery Aneurysms and Pseudoaneurysms—Should They All be Managed by Endovascular Techniques? *Ann Vasc Dis* 2013; **6**: 687-693 [PMID: 24386016 DOI: 10.3400/avd.ra.13-00045]
41 **Rai P**, Kc H, Goel A, Aggarwal R, Sharma M. Endoscopic ultrasound-guided coil and glue for treatment of splenic artery pseudo-aneurysm: new kid on the block! *Endosc Int Open* 2018; **6**: E821-E825 [PMID: 29978000 DOI: 10.1055/a-0608-4402]
42 **Rudnick SR**, Conway JD, Russo MW. Current state of endohepatology: Diagnosis and treatment of portal hypertension and its complications with endoscopic ultrasound. *World J Hepatol* 2021; **13**: 887-895 [PMID: 34552695 DOI: 10.4254/wjh.v13.i8.887]
43 **Chapman CG**, Waxman I. EUS-guided portal vein sampling. *Endosc Ultrasound* 2018; **7**: 240-245 [PMID: 30117486 DOI: 10.4103/eus.eus_28_18]
44 **Chapman CG**, Waxman I. EUS-Guided Portal Venous Sampling of Circulating Tumor Cells. *Curr Gastroenterol Rep* 2019; **21**: 68 [PMID: 31813055 DOI: 10.1007/s11894-019-0733-2]
45 **Groszmann R**, Vorobioff JD, Gao H. Measurement of portal pressure: when, how, and why to do it. *Clin Liver Dis* 2006; **10**: 499-512, viii [PMID: 17162225 DOI: 10.1016/j.cld.2006.08.005]
46 **Zhang W**, Peng C, Zhang S, Huang S, Shen S, Xu G, Zhang F, Xiao J, Zhang M, Zhuge Y, Wang L, Zou X, Lv Y. EUS-guided portal pressure gradient measurement in patients with acute or subacute portal hypertension. *Gastrointest Endosc* 2021; **93**: 565-572 [PMID: 32615178 DOI: 10.1016/j.gie.2020.06.065]
47 **Hajifathalian K**, Westerveld D, Kaplan A, Dawod E, Herr A, Ianelli M, Saggese A, Kumar S, Fortune BE, Sharaiha RZ. Simultaneous EUS-guided portosystemic pressure measurement and liver biopsy sampling correlate with clinically meaningful outcomes. *Gastrointest Endosc* 2022; **95**: 703-710 [PMID: 34890694 DOI: 10.1016/j.gie.2021.11.037]
48 **Garg R**, Rustagi T. Endoscopic Ultrasound-guided Portal Venous Access: Diagnostic and Therapeutic Implications. *J Clin Gastroenterol* 2017; **51**: 677-682 [PMID: 28742731 DOI: 10.1097/MCG.0000000000000897]
49 **Loffroy R**, Favelier S, Chevallier O, Estivalet L, Genson PY, Pottecher P, Gehin S, Krausé D, Cercueil JP. Preoperative portal vein embolization in liver cancer: indications, techniques and outcomes. *Quant Imaging Med Surg* 2015; **5**: 730-739 [PMID: 26682142 DOI: 10.3978/j.issn.2223-4292.2015.10.04]
50 **Armonis A**, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis? *Hepatology* 1997; **25**: 245-248 [PMID: 8985299 DOI: 10.1053/jhep.1997.v25.ajhep0250245]
51 **Lai L**, Poneros J, Santilli J, Brugge W. EUS-guided portal vein catheterization and pressure measurement in an animal model: a pilot study of feasibility. *Gastrointest Endosc* 2004; **59**: 280-283 [PMID: 14745408 DOI: 10.1016/s0016-5107(03)02544-6]
52 **Giday SA**, Ko CW, Clarke JO, Shin EJ, Magno P, Jagannath SB, Buscaglia JM, Kantsevoy SV. EUS-guided portal vein carbon dioxide angiography: a pilot study in a porcine model. *Gastrointest Endosc* 2007; **66**: 814-819 [PMID: 17905028 DOI: 10.1016/j.gie.2007.05.056]
53 **Kayar Y**, Turkdogan KA, Baysal B, Unver N, Danalioglu A, Senturk H. EUS-guided FNA of a portal vein thrombus in hepatocellular carcinoma. *Pan Afr Med J* 2015; **21**: 86 [PMID: 26491529 DOI: 10.11604/pamj.2015.21.86.6991]
54 **Gimeno Garcia AZ**, Aparicio JR, Barturen A, Moreno M, Nicolas-Perez D, Quintero E. Short article: Endoscopic ultrasound-guided fine-needle aspiration of portal vein thrombosis in patients with chronic liver disease and suspicion of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2018; **30**: 418-423 [PMID: 29420366 DOI: 10.1097/MEG.0000000000001094]
55 **Zhang WY**, Li ZS, Jin ZD. Endoscopic ultrasound-guided ethanol ablation therapy for tumors. *World J Gastroenterol* 2013; **19**: 3397-3403 [PMID: 23801831 DOI: 10.3748/wjg.v19.i22.3397]
56 **Moyer MT**, Maranki JL, DeWitt JM. EUS-Guided Pancreatic Cyst Ablation: a Clinical and Technical Review. *Curr Gastroenterol Rep* 2019; **21**: 19 [PMID: 31016391 DOI: 10.1007/s11894-019-0686-5]
57 **Faigel D**, Lake D, Landreth T, Kelman C, Marler R. Endoscopic ultrasonography-guided portal injection chemotherapy for hepatic metastases. *Endosc Ultrasound* 2014; **3**: S1 [PMID: 26425503]
58 **Faigel DO**, Lake DF, Landreth TL, Kelman CC, Marler RJ. EUS-guided portal injection chemotherapy for treatment of hepatic metastases: feasibility in the acute porcine model. *Gastrointest Endosc* 2016; **83**: 444-446 [PMID: 26358330 DOI: 10.1016/j.gie.2015.08.064]

59 **Philips CA**, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P. Beyond the scope and the glue: update on evaluation and management of gastric varices. *BMC Gastroenterol* 2020; **20**: 361 [PMID: 33126847 DOI: 10.1186/s12876-020-01513-7]

60 **Yokoyama K**, Miyayama T, Uchida Y, Fukuda H, Yamauchi R, Tsuchiya N, Umeda K, Takata K, Tanaka T, Inomata S, Morihara D, Takeyama Y, Shakado S, Sakisaka S, Hirai F. Novel Endoscopic Therapy for Gastric Varices Using Direct Forward-Viewing Endoscopic Ultrasonography. *Case Rep Gastroenterol* 2021; **15**: 28-34 [PMID: 33613160 DOI: 10.1159/000510132]

61 **Robb PM**, Yeaton P, Bishop T, Wessinger J. Endoscopic Ultrasound Guided Embolization of a Pancreatic Pseudoaneurysm. *Gastroenterology Res* 2012; **5**: 239-241 [PMID: 27785215 DOI: 10.4021/gr500w]

62 **Gamanagatti S**, Thingujam U, Garg P, Nongthombam S, Dash NR. Endoscopic ultrasound guided thrombin injection of angiographically occult pancreatitis associated visceral artery pseudoaneurysms: Case series. *World J Gastrointest Endosc* 2015; **7**: 1107-1113 [PMID: 26421108 DOI: 10.4253/wjge.v7.i13.1107]

63 **Jhajharia A**, Wanjari S, Ashdhir P, Sharma D, Pokharna R, Nijhawan S. Endoscopic ultrasound-guided thrombin injection for management of visceral artery pseudoaneurysm: A novel approach. *Indian J Gastroenterol* 2018; **37**: 271-275 [PMID: 29971689 DOI: 10.1007/s12664-018-0865-6]

64 **Gunjan D**, Gamanagatti S, Garg P. Endoscopic ultrasonography-guided obliteration of a left inferior phrenic artery pseudoaneurysm in a patient with alcoholic chronic pancreatitis. *Endoscopy* 2018; **50**: 449-450 [PMID: 29351702 DOI: 10.1055/s-0043-124867]

65 **Sharma M**, Somani P, Sunkara T, Prajapati R, Talele R. Endoscopic ultrasound-guided coil embolization and thrombin injection of a bleeding gastroduodenal artery pseudoaneurysm. *Endoscopy* 2019; **51**: E36-E37 [PMID: 30537784 DOI: 10.1055/a-0790-8134]

66 **Buscaglia JM**, Shin EJ, Clarke JO, Giday SA, Ko CW, Thuluvath PJ, Magno P, Dray X, Kantsevoy SV. Endoscopic retrograde cholangiopancreatography, but not esophagogastroduodenoscopy or colonoscopy, significantly increases portal venous pressure: direct portal pressure measurements through endoscopic ultrasound-guided cannulation. *Endoscopy* 2008; **40**: 670-674 [PMID: 18561105 DOI: 10.1055/s-2008-1077341]

67 **Huang JY**, Samarasena JB, Tsujino T, Chang KJ. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device *vs* standard transjugular approach: a comparison animal study. *Gastrointest Endosc* 2016; **84**: 358-362 [PMID: 26945557 DOI: 10.1016/j.gie.2016.02.032]

68 **Schulman AR**, Thompson CC, Ryou M. EUS-guided portal pressure measurement using a digital pressure wire with real-time remote display: a novel, minimally invasive technique for direct measurement in an animal model. *Gastrointest Endosc* 2016; **83**: 817-820 [PMID: 26684600 DOI: 10.1016/j.gie.2015.11.038]

69 **Huang JY**, Samarasena JB, Tsujino T, Lee J, Hu KQ, McLaren CE, Chen WP, Chang KJ. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. *Gastrointest Endosc* 2017; **85**: 996-1001 [PMID: 27693644 DOI: 10.1016/j.gie.2016.09.026]

70 **Rustagi T**, Gleeson FC, Chari ST, Abu Dayyeh BK, Farnell MB, Iyer PG, Kendrick ML, Pearson RK, Petersen BT, Rajan E, Topazian MD, Truty MJ, Vege SS, Wang KK, Levy MJ. Remote malignant intravascular thrombi: EUS-guided FNA diagnosis and impact on cancer staging. *Gastrointest Endosc* 2017; **86**: 150-155 [PMID: 27773725 DOI: 10.1016/j.gie.2016.10.025]

71 **Moreno M**, Gimeno-García AZ, Corriente MM, Nicolás-Pérez D, Brito-García A, García-Castro C, Quintero E. EUS-FNA of a portal vein thrombosis in a patient with a hidden hepatocellular carcinoma: confirmation technique after contrast-enhanced ultrasound. *Endoscopy* 2014; **46** Suppl 1 UCTN: E590-E591 [PMID: 25502254 DOI: 10.1055/s-0034-1390734]

72 **Michael H**, Lenza C, Gupta M, Katz DS. Endoscopic Ultrasound -guided Fine-Needle Aspiration of a Portal Vein Thrombus to Aid in the Diagnosis and Staging of Hepatocellular Carcinoma. *Gastroenterol Hepatol (N Y)* 2011; **7**: 124-129 [PMID: 21475421]

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Retrospective Study

Pediatric endoscopy across multiple clinical settings: Efficiency and adverse events

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Abstract

BACKGROUND

Endoscopic procedures are becoming increasingly important for the diagnosis and treatment of gastrointestinal disorders during childhood, and have evolved from a more infrequent inpatient procedure in the operating room to a routine outpatient procedure conducted in multiple care settings. Demand for these procedures is rapidly increasing and thus there is a need to perform them in an efficient manner. However, there are little data comparing the efficiency of pediatric endoscopic procedures in diverse clinical environments. We hypothesized that there are significant differences in efficiency between settings.

AIM

To compare the efficiency and examine adverse effects of pediatric endoscopic procedures across three clinical settings.

METHODS

A retrospective chart review was conducted on 1623 cases of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy performed between January 1, 2014 and May 31, 2018 by 6 experienced pediatric gastroenterologists in three different clinical settings, including a tertiary care hospital operating room, community hospital operating room, and free-standing pediatric ambulatory endoscopy center at a community hospital. The following strict guidelines were used to schedule patients at all three locations: age greater than 6 mo; American

Society of Anesthesiologists class 1 or 2; normal craniofacial anatomy; no anticipated therapeutic intervention (*e.g.*, foreign body retrieval, stricture dilation); and, no planned or anticipated hospitalization post-procedure. Data on demographics, times, admission rates, and adverse events were collected. Endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite) were calculated to assess efficiency.

RESULTS

In total, 58% of the cases were performed in the tertiary care operating room. The median age of patients was 12 years and the male-to-female ratio was nearly equal across all locations. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 ± 21.5 min *vs* 51.4 ± 18.9 min, $P < 0.001$) and 7 min longer compared to the endoscopy center (*vs* 56.6 ± 19.3 min, $P < 0.001$). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 ± 39.9 min *vs* 122.3 ± 39.5 min, $P < 0.001$) and 9 min longer compared to the endoscopy center (*vs* 124.9 ± 37.9 min; $P < 0.001$). When comparing endoscopist and patient times for EGD and EGD/colonoscopies among the three locations, endoscopist, and patient times were again shorter in the community hospital and endoscopy center compared to the tertiary care operating room. Adverse events from procedures occurred in 0.1% ($n = 2$) of cases performed in the tertiary care operating room, with 2.2% ($n = 35$) of cases from all locations having required an unplanned admission after the endoscopy for management of a primary GI disorder.

CONCLUSION

Pediatric endoscopic procedures can be conducted more efficiently in select patients in a community operating room and endoscopy center compared to a tertiary care operating room.

Key Words: Pediatric endoscopy; Efficiency; Adverse events; Tertiary care operating room; Community operating room; Endoscopy center

Core Tip: This was a retrospective study where we compared the efficiency of pediatric endoscopic procedures in a tertiary care operating room, community operating room, and endoscopy center and secondarily examined adverse events of procedures across these settings. We found that with using strict, identical scheduling guidelines for all locations, undergoing esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy at the community hospital room and endoscopy center was significantly faster for the patient and endoscopist when compared to the tertiary care operating room. The rate of adverse events was similar across all three locations.

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INTRODUCTION

Endoscopic procedures are crucial for the diagnosis, treatment, and surveillance of gastrointestinal disorders in children. Moreover, the demand for these services is increasing[1]. Along with the increased utilization, the clinical setting in which these procedures are performed is changing and are now being performed as outpatient procedures conducted in multiple clinical settings[1-5]. While they are most commonly performed in operating rooms within tertiary care institutions or dedicated pediatric endoscopy suites, many endoscopies are being performed in outpatient centers[3].

With the overall increasing demand for endoscopic procedures, there is a need to perform them in an efficient manner. Locations outside of pediatric tertiary care centers have the potential to accommodate a high volume of patients due to the elimination of emergent procedures and scheduling of lower risk patients. Clinical reports regarding the development of adult and pediatric endoscopy units have focused on defining metrics used to assess efficiency, ranging from productivity metrics such as the number of procedures per hour to operational metrics such as turnover time[2,6]. Several adult studies

have shown turnover time, the time between procedures, varies among clinical settings (*e.g.*, hospitals, ambulatory surgery centers) and is the main factor contributing to delay of procedures and the primary predictor of the number performed per hour[7,8]. However, there are substantial differences in the workflow between pediatric and adult patients that limit the applicability of adult metrics to the pediatric population[9-11]. There is no universal consensus on how efficiency can be optimized in pediatrics and scant information on its application in outpatient endoscopy centers.

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings. Secondarily, we assessed adverse events associated with endoscopic procedures performed in select pediatric patients at non-tertiary care facilities.

MATERIALS AND METHODS

We conducted a retrospective chart review of patients cared for by the Division of Pediatric Gastroenterology, Hepatology & Nutrition at University Hospitals Rainbow Babies and Children's Hospital (Cleveland, OH, United States) who underwent an outpatient esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy between January 1, 2014 and May 31, 2018. This study was approved by the local institutional review board.

Locations

During the period of this study, the Division performed endoscopies at three locations, including pediatric tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. All locations were staffed by the same pediatric anesthesia and endoscopy personnel. The tertiary care hospital had a single dedicated operating room for inpatient and outpatient procedures; the endoscopist did not perform endoscopies outside of the assigned operating room. The anesthesiologist assigned to the endoscopy cases in the tertiary care operating room potentially covered other surgical cases occurring simultaneously in other rooms. The community hospital operating room and the community pediatric ambulatory endoscopy unit consisted of one procedure room. The rooms in these latter two settings were dedicated to the outpatient endoscopic procedures; however, different from the tertiary care hospital, each room had a pediatric anesthesiologist assigned exclusively to that location. Endoscopic procedures were scheduled back-to-back: 60 min for combined EGD and colonoscopies at all locations; 60 min for EGD at the tertiary care operating room; and, 30 min for EGD at the community hospital and endoscopy center.

Endoscopic case characteristics

During the period of this study, our institution followed strict guidelines to schedule patients at the community locations. These guidelines were developed through consensus opinion among the pediatric gastroenterologists, pediatric anesthesiologists, and endoscopy personnel. Patients were eligible for these locations if the following criteria were met: age greater than 6 mo; American Society of Anesthesiologists class 1 (healthy person) or 2 (mild systemic disease); normal craniofacial anatomy; no anticipated therapeutic intervention (*e.g.*, foreign body retrieval, stricture dilation, control of bleeding, variceal ligation); and, no planned or anticipated hospitalization post-procedure. Additionally, urgent or emergent cases were not performed at these locations. For this analysis, we used the same criteria to select patients undergoing endoscopy at the tertiary care hospital operating room for comparison. Also, the last case of each day was excluded from analysis as we are unable to calculate the endoscopist time. Cases that preceded inpatient procedures at the tertiary care operating room also were excluded to ensure timing and scheduling of cases were as similar as possible at all three locations.

Physicians

We reviewed only those cases performed by the pediatric gastroenterologists who performed endoscopies at the tertiary care operating room and one of the other locations. These 6 pediatric gastroenterologists were board certified, experienced endoscopists.

Data collection

We extracted data for all endoscopic procedures meeting the above criteria. Fewer cases were performed at the community ambulatory endoscopy center as compared to the other locations. To control for this disparity, cases performed at that site were matched by physician with cases performed at the tertiary care operating room; the cases from the tertiary care operating room were selected chronologically at the start of a calendar year until the number of cases between the two locations were approximately equal for each of those three physicians. Patient demographics, time variables (patient registration, patient and physician entering operating room, and patient exiting operating room), procedural or anesthesia complications, unexpected admissions, and fellow participation in the procedure were extracted from the medical record.

Adverse events were defined as endoscopic complications (*e.g.*, gastrointestinal bleeding or perforation), sedation and cardiopulmonary complications (*e.g.*, respiratory failure, need for intubation), any cause necessitating unintended emergency department visit or hospital admission, and hospital admission for ongoing medical care. We included hospital admission for ongoing medical care as an adverse event as patients undergoing endoscopy in the community settings would require transportation to the tertiary care hospital for care (also see guidelines for scheduling above).

Endoscopist time (ET) and patient time (PT) were calculated for each case. ET was defined as elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering. PT was defined as elapsed time from patient registration to that patient exiting the operating room or endoscopy suite. These times by definition include room turnover time and provide estimates of real time for the physician and patient.

Statistical analyses

Statistical analyses were performed by a trained statistician. Descriptive statistics were generated for each of the variables collected. Categorical data are reported as frequencies and percentages and when appropriate, χ^2 analyses were used. Continuous data are reported as numbers (n), means and standard deviations, and medians, and when appropriate, analysis of variance and unpaired t-test were used for analyses. Unless otherwise stated, statistical testing was conducted using two-sided alternatives with a type I error level of 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) was used to generate the statistics.

RESULTS

We identified 1623 cases (Table 1). Just over half were performed in the tertiary care operating room. The fewest were performed in the community ambulatory endoscopy center (7.6%). All cases were performed under monitored anesthesia care using propofol. The median age of the patients was 12 years, and the male-to-female ratio was nearly equal. There were no differences in age or sex among the cases performed at each endoscopy site or by each physician. Fellows participated in 38% of cases, with the highest percentage in the tertiary care operating room.

Efficiency

We found the tertiary hospital operating room to be the least efficient site to perform endoscopy even controlling for physician, patient age, fellow participation, and type of procedure (Table 2). The ET in the tertiary hospital operating room was 11.9 min longer than in the community operating room ($P < 0.001$) and 6.7 min longer than in the community endoscopy center ($P < 0.001$). Likewise, the PT at the tertiary care operating room was 11.2 min longer than the community operating room ($P < 0.001$) and 8.3 min longer than the endoscopy center ($P < 0.001$).

We compared the ET and PT for EGD and EGD/colonoscopies between the specific locations given that differences in case mix amongst locations may have affected the results, and confirmed the community operating room and endoscopy center were more efficient for each of these types of procedures (Table 3). We further evaluated the times based on individual physicians. Compared to the times in the tertiary care operating room, all of the physicians had a shorter ET in the community operating room and endoscopy center, and 5 of the 6 physicians had a shorter PT in the community operating room and endoscopy center compared to the tertiary care operating room (Table 4). The 1 physician (physician 6 in Table 4) with the longer PT in the community operating room compared to the tertiary care operating room (136.5 ± 35.7 *vs* 135.9 ± 41.8), also had the longest patient and endoscopist times overall. We did not calculate the statistical significance of ET and PT between physicians because the proportions of cases across locations were not equal.

Using analysis of variance, fellow participation did not significantly affect endoscopist or patient time when considering all cases, and we found that location accounted for the affect ($P < 0.001$). Fellow participation in the tertiary care operating room was associated with longer PT and ET, and the presence of a fellow overall resulted in the longest times.

Adverse events

Unplanned admissions following an endoscopic procedure occurred for a small number of patients (all locations, 2.2%, $n = 35$). The majority of these ($n = 33$) were for further management of a primary GI disease (*e.g.*, inflammatory bowel disease) and not an endoscopic or anesthesia related complication. Patients were less frequently admitted for any reason from each of the two community-based locations as compared to the tertiary operating room (community operating room, 0.2% of total at site, $n = 4$; community endoscopy center 0.1% of total at site, $n = 1$; tertiary hospital operating room, 1.8% of total at site, $n = 30$). Endoscopic complications occurred in two of the evaluated cases (0.1%). Both involved patients undergoing an EGD and colonoscopy in the tertiary hospital operating room. One patient was admitted to the pediatric intensive care unit for management of gastrointestinal bleeding requiring a blood transfusion and the other to the general medical unit for observation for concern of a

Table 1 Demographics, procedures, and fellow participation by location

Characteristic	Value			
	Tertiary care OR	Community OR	Endoscopy center	Overall
Age, yr (median)[1]	11	12	12	12
Male, *n* (%)[1]	494 (52.4)	268 (48.0)	63 (51.2)	825 (50.8)
EGD, *n* (%)	537 (57)	283 (50.7)	56 (45.5)	876 (54)
EGD/colonoscopy, *n* (%)	405 (43)	275 (49.3)	67 (54.4)	747 (46)
Total procedures, *n* (%)	942 (100)	558 (100)	123 (100)	1623 (100)
Fellow participation, *n* (%)	499 (53)	89 (16)	25 (20)	613 (38)

[1]There were no significant differences in the distribution of age and sex across the clinical settings. EGD: Esophagogastroduodenoscopy; OR: Operating room.

Table 2 Endoscopist time and patient time in minutes by location

	Tertiary care OR	Community OR	Endoscopy center	*P* value[1]
ET (mean ± SD)	63.3 ± 21.5	51.4 ± 18.9	56.6 ± 19.3	< 0.001
PT (mean ± SD)	133.2 ± 39.9	122.0 ± 39.5	124.9 ± 37.9	< 0.001

[1]ANOVA controlling for physician, patient age, fellow participation, and type of procedures. ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

Table 3 Endoscopist time and patient time in minutes by location and procedure

	Procedure	Tertiary care OR	Community OR	Endoscopy center	*P* value
ET (mean ± SD)	EGD	63.2 ± 20.2	39.6 ± 13.6	45.0 ± 13.3	< 0.001
	EGD/colonoscopy	75.6 ± 17.3	63.4 ± 16.0	66.3 ± 18.0	< 0.001
PT (mean ± SD)	EGD	121.4 ± 39.0	107.7 ± 34.2	112.9 ± 31.8	< 0.001
	EGD/colonoscopy	148.4 ± 36.1	137.4 ± 38.9	135.0 ± 39.5	< 0.001

ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

gastrointestinal bleed. A fellow was present during the endoscopy for one of the two complications.

DISCUSSION

The goals of our study were to assess the efficiency of pediatric endoscopic procedures in different clinical settings and to evaluate whether the performance of these procedures in a community setting was associated with an excess of adverse events. Changing indications for endoscopic procedures and a steady increase in gastrointestinal disease burden in this population resulted in an increase in demand for these procedures to which the medical community must adapt[1]. From 2011 to 2018, our institution expanded from three to nine pediatric gastroenterologists and the number of completed endoscopic procedures more than doubled. Improving efficiency without compromising safety is essential to accommodate the increased demand of endoscopic procedures and prevent delays in diagnosis and treatment.

We found it was more efficient to perform endoscopic procedures in two community-based locations compared to a tertiary care operating room. As our measures of efficiency, we used ET to measure time between cases for the endoscopist including room turn-over and other system delays and PT to include time spent at the hospital or endoscopy unit except for the time post-endoscopy in recovery. The ET was 6.7 to 11.9 min and the PT was 8.3 min to 11.2 min shorter in the endoscopy center and community operating room, respectively compared to the tertiary care operating room. The differences in ET and PT are likely due to factors specific to the tertiary care location rather than type or complexity of the case

Table 4 Endoscopist time and patient time in min by physician

Physician	Endoscopist time			Patient time		
	Tertiary care OR	Community OR	Endoscopy center	Tertiary care OR	Community OR	Endoscopy center
1	61.9 ± 23.1	53.2 ± 20.2		131.1 ± 38.3	126.7 ± 44.9	
2	63.9 ± 17.4	45.5 ± 14.5		142.9 ± 38.9	120.8 ± 34.9	
3	63.4 ± 22.4	45.5 ± 14.5		128.3 ± 42.4	110.2 ± 31.1	
4	64.4 ± 19.1		47.8 ± 13.5	126.0 ± 36.7		113.6 ± 38.4
5	63.4 ± 16.9		59.3 ± 19.5	160.8 ± 28.8		128.0 ± 33.7
6	68.6 ± 22.5		65.4 ± 20.7	135.9 ± 41.8		136.5 ± 35.7

Data are presented as mean ± SD. OR: Operating room.

as we controlled for these variables. If we did not employ the same criteria used to schedule patients in the community locations to select the comparator patients at the tertiary care operating room, the times in the tertiary care operating room would be longer as emergent and complex cases (*e.g.*, variceal banding, multiple comorbidities) would be included and likely result in delays.

Several studies have described factors that can impact efficiency of endoscopic procedures[7,8,12,13]. These may be related to the patient (*e.g.*, late to registration or no-show), physician (*e.g.*, late to procedure), or support personnel (*e.g.*, room turnover time). While we did not directly determine causes of the differences in efficacy besides fellow participation, our results support previous findings that decreases in efficiency at the tertiary care center are less likely to be solely related to patient or endoscopist behavior as ET and PT were almost always individually faster at the community locations. However, the endoscopist's efficiency may become a limiting factor after a certain point. For example, physician 6 had comparatively longer ET and PT times at the tertiary care center and at the endoscopy center and these were the longest times overall. This may explain why the community OR had lower ET and PT times compared to the endoscopy center, although both community locations were still more efficient when compared to the tertiary care center. Overall, the loss in efficiency may be a system problem, where possible location specific factors include room turnover, availability of anesthesiology staff, or endoscopist delayed with other tasks. Trainee participation has been shown to adversely impact efficiency by prolonging procedures[8]. In our study, while fellow participation did not affect efficiency when considering all cases included, their participation specifically in the tertiary care operating room was associated with longer ET and PT. This might be due to our institution's practice of only having senior fellows participate in endoscopy sessions at the community sites. First year fellows participate in endoscopies at the tertiary care operating room.

Regarding anesthesiologist participation during endoscopic procedures, they are often being shared with other operating rooms at the tertiary care center, which may delay procedural start time. Having a dedicated anesthesiologist at the community locations eliminates this problem. It is important to note, monitored anesthesia care with propofol was used in all of the patients in this study and has been shown to be safe and efficient due to its rapid sedation and recovery time[14,15]. Thus, our data may not translate to centers using agents other than propofol or have non-anesthesiologist staff perform sedation.

Practically, the accumulated saved time at the community locations on a typical 8-h day could reach 90 min allowing for at least two additional cases per day. Adjustments to scheduling and allotted time for procedures may help meet the increasing demand by allowing more procedures to be performed in a day. Other direct benefits from performing endoscopic procedures more efficiently are increases in patient satisfaction and institutional revenue. Performing a given number of procedures within a shorter time period will directly impact the physician's ability to complete other tasks.

We evaluated adverse events defined as endoscopic complications, anesthesia and respiratory complications, and unintended admissions occurring within 72 h of the procedure. We did not evaluate mild adverse events (*i.e.*, nausea, throat pain). There were no procedural, anesthesia and respiratory complications at the community hospital and the ambulatory endoscopy center. Although there were fewer adverse events within the community locations, the number of cases included in this study is too low to determine whether endoscopies in these locations are safer than in a tertiary care facility[16-18]. To make this determination, a large multi-institutional study performed over several years is required. Thus, we only described our experience.

The major strengths of our study were the ability to compare cases performed by each endoscopist between two different locations as well as to compare the ET and PT among all 6 physicians at all three locations. Endoscopic procedures were performed in three clearly delineated locations with the same support staff and the use of strict criteria for scheduling of patients within the community centers. This study due to its retrospective nature has few weaknesses. All cases performed in the tertiary operating

room were not used in the analysis to allow us to match the relatively smaller number of cases at the community sites. However, given that the cases were all conducted within a similar time period and the physicians were all experienced endoscopists, the excluded cases are unlikely to reflect a bias in the results. There was a difference in the allotted time for EGD between the tertiary care operating room and community locations, however we do not believe this had an impact on the study as the procedures were scheduled one after the other with the guidance to perform the subsequent procedure once the operating room was available. Also, the study is underpowered to detect true differences in the rates of adverse events.

CONCLUSION

In conclusion, we found that in select pediatric patient populations, endoscopic procedures can be performed more efficiently in non-tertiary care centers. These data may help future guidelines on building efficient outpatient pediatric endoscopy suites. Further investigation is needed to understand why these procedures are more efficient at community locations. Also, our data forms a foundation upon which further studies can be performed to evaluate whether there is an increased risk to the patient with this practice. Being able to provide more efficient care in a convenient location for selected patients can increase satisfaction while accommodating the increase need for such procedures.

ARTICLE HIGHLIGHTS

Research background

There has been an increase in pediatric endoscopic procedures over time and an increased demand to perform them efficiently. These procedures are now being performed in more diverse clinical settings, from tertiary care operating rooms to ambulatory centers. Data is lacking with regards to safety and efficiency of these procedures across multiple clinical settings which is needed information as the pediatric endoscopic landscape diversifies.

Research motivation

We aimed to understand efficiency and adverse rate events of pediatric endoscopic procedures across multiple clinical settings as there is a paucity of this data in the literature. This research could help lay the foundation for guidelines of building outpatient pediatric endoscopy suites or ambulatory centers.

Research objectives

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings, particularly ambulatory centers as compared to a tertiary care operating room. We also assessed adverse events associated with endoscopic procedures performed across these clinical settings.

Research methods

A retrospective chart review was conducted of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopies performed over a 4 year period by 6 experienced gastroenterologists in three settings; a tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. Demographics, times, admission rates and adverse events were collected and efficiency was measured in endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite). Statistical analyses were performed by a trained statistician and descriptive statistics were generated for each of the variables collected.

Research results

The majority of the cases were performed at the tertiary care operating room. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 ± 21.5 min *vs* 51.4 ± 18.9 min; $P < 0.001$) and 7 min longer compared to the endoscopy center (*vs* 56.6 ± 19.3 min; $P < 0.001$). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 ± 39.9 min *vs* 122.3 ± 39.5 min; $P < 0.001$) and 9 min longer compared to the endoscopy center (*vs* 124.9 ± 37.9 min, $P < 0.001$). Adverse events occurred in 0.1% of cases performed in the tertiary care operating room.

Research conclusions

We found that it was more efficient to perform EGD and colonoscopies at a community hospital

operating room and a free-standing pediatric ambulatory endoscopy center at a community hospital when compared to a tertiary care operating room in a select pediatric population. There was not an increased adverse event rate that we observed at these satellite locations when compared to the tertiary care operating room. Being able to perform these procedures safely and efficiently in multiple clinical settings may help meet the growing demand of endoscopic procedures in children.

Research perspectives

This research showed that pediatric endoscopic procedures are efficient in multiple clinical settings in a select pediatric population. Larger, prospective studies are needed to validate what we have found and to better assess safety. Our research could help lay the foundation for future guidelines on building efficient outpatient pediatric endoscopy suites.

FOOTNOTES

Author contributions: Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS contributed equally to this work; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS designed the research study; Crawford E and Khalili AS performed the research; Crawford E and Apperson-Hansen C analyzed the data; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS wrote the manuscript; all authors have read and approved the final manuscript.

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REFERENCES

1 **Franciosi JP**, Fiorino K, Ruchelli E, Shults J, Spergel J, Liacouras CA, Leonard M. Changing indications for upper endoscopy in children during a 20-year period. *J Pediatr Gastroenterol Nutr* 2010; **51**: 443-447 [PMID: 20562722 DOI: 10.1097/MPG.0b013e3181d67bee]
2 **Pall H**, Lerner D, Khlevner J, Reynolds C, Kurowski J, Troendle D, Utterson E, Evans PM, Brill H, Wilsey M, Fishman DS. Developing the Pediatric Gastrointestinal Endoscopy Unit: A Clinical Report by the Endoscopy and Procedures Committee. *J Pediatr Gastroenterol Nutr* 2016; **63**: 295-306 [PMID: 26974415 DOI: 10.1097/MPG.0000000000001189]
3 **Lerner DG**, Pall H. Setting up the Pediatric Endoscopy Unit. *Gastrointest Endosc Clin N Am* 2016; **26**: 1-12 [PMID: 26616893 DOI: 10.1016/j.giec.2015.08.008]
4 **Friedt M**, Welsch S. An update on pediatric endoscopy. *Eur J Med Res* 2013; **18**: 24 [PMID: 23885793 DOI: 10.1186/2047-783X-18-24]
5 **Gilger MA**. Gastroenterologic endoscopy in children: past, present, and future. *Curr Opin Pediatr* 2001; **13**: 429-434 [PMID: 11801888 DOI: 10.1097/00008480-200110000-00008]
6 **Day LW**, Belson D. Studying and Incorporating Efficiency into Gastrointestinal Endoscopy Centers. *Gastroenterol Res Pract* 2015; **2015**: 764153 [PMID: 26101525 DOI: 10.1155/2015/764153]
7 **Zamir S**, Rex DK. An initial investigation of efficiency in endoscopy delivery. *Am J Gastroenterol* 2002; **97**: 1968-1972 [PMID: 12190162 DOI: 10.1111/j.1572-0241.2002.05909.x]
8 **Yong E**, Zenkova O, Saibil F, Cohen LB, Rhodes K, Rabeneck L. Efficiency of an endoscopy suite in a teaching hospital: delays, prolonged procedures, and hospital waiting times. *Gastrointest Endosc* 2006; **64**: 760-764 [PMID: 17055870 DOI: 10.1016/j.gie.2006.02.047]
9 **Kramer RE**, Walsh CM, Lerner DG, Fishman DS. Quality Improvement in Pediatric Endoscopy: A Clinical Report From

the NASPGHAN Endoscopy Committee. *J Pediatr Gastroenterol Nutr* 2017; **65**: 125-131 [PMID: 28644360 DOI: 10.1097/MPG.0000000000001592]

10 **Forget S**, Walsh C. Pediatric endoscopy: need for a tailored approach to guidelines on quality and safety. *Can J Gastroenterol* 2012; **26**: 735 [PMID: 23061068 DOI: 10.1155/2012/594310]

11 **ASGE Standards of Practice Committee**, Lightdale JR, Acosta R, Shergill AK, Chandrasekhara V, Chathadi K, Early D, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Hwang JH, Kashab M, Muthusamy VR, Pasha S, Saltzman JR, Cash BD; American Society for Gastrointestinal Endoscopy. Modifications in endoscopic practice for pediatric patients. *Gastrointest Endosc* 2014; **79**: 699-710 [PMID: 24593951 DOI: 10.1016/j.gie.2013.08.014]

12 **Tomer G**, Choi S, Montalvo A, Sutton S, Thompson J, Rivas Y. Improving the timeliness of procedures in a pediatric endoscopy suite. *Pediatrics* 2014; **133**: e428-e433 [PMID: 24446444 DOI: 10.1542/peds.2013-2316]

13 **Mani J**, Franklin L, Pall H. Impact of Pre-Procedure Interventions on No-Show Rate in Pediatric Endoscopy. *Children (Basel)* 2015; **2**: 89-97 [PMID: 27417352 DOI: 10.3390/children2010089]

14 **Dar AQ**, Shah ZA. Anesthesia and sedation in pediatric gastrointestinal endoscopic procedures: A review. *World J Gastrointest Endosc* 2010; **2**: 257-262 [PMID: 21160616 DOI: 10.4253/wjge.v2.i7.257]

15 **Sipe BW**, Rex DK, Latinovich D, Overley C, Kinser K, Bratcher L, Kareken D. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002; **55**: 815-825 [PMID: 12024134 DOI: 10.1067/mge.2002.124636]

16 **Thakkar K**, El-Serag HB, Mattek N, Gilger M. Complications of pediatric colonoscopy: a five-year multicenter experience. *Clin Gastroenterol Hepatol* 2008; **6**: 515-520 [PMID: 18356115 DOI: 10.1016/j.cgh.2008.01.007]

17 **Hsu EK**, Chugh P, Kronman MP, Markowitz JE, Piccoli DA, Mamula P. Incidence of perforation in pediatric GI endoscopy and colonoscopy: an 11-year experience. *Gastrointest Endosc* 2013; **77**: 960-966 [PMID: 23433599 DOI: 10.1016/j.gie.2012.12.020]

18 **Thakkar K**, El-Serag HB, Mattek N, Gilger MA. Complications of pediatric EGD: a 4-year experience in PEDS-CORI. *Gastrointest Endosc* 2007; **65**: 213-221 [PMID: 17258979 DOI: 10.1016/j.gie.2006.03.015]

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic ultrasound diagnostic gain over computed tomography and magnetic resonance cholang-iopancreatography in defining etiology of idiopathic acute pancreatitis

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Abstract

BACKGROUND

About 10%-30% of acute pancreatitis remain idiopathic (IAP) even after clinical and imaging tests, including abdominal ultrasound (US), contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP). This is a relevant issue, as up to 20% of patients with IAP have recurrent episodes and 26% of them develop chronic pancreatitis. Few data are available on the role of EUS in clarifying the etiology of IAP after failure of one or more cross-sectional techniques.

AIM

To evaluate the diagnostic gain after failure of one or more previous cross-sectional exams.

METHODS

We retrospectively collected data about consecutive patients with AP and at least one negative test between US, CECT and MRCP, who underwent linear EUS between January 2017 and December 2020. We investigated the EUS diagnostic yield and the EUS diagnostic gain over different combinations of these cross-

sectional imaging techniques for the etiologic diagnosis of AP. Types and frequency of EUS diagnosis were also analyzed, and EUS diagnosis was compared with the clinical parameters. After EUS, patients were followed-up for a median of 31.5 mo to detect cases of pancreatitis recurrence.

RESULTS

We enrolled 81 patients (63% males, mean age 61 ± 18, 23% with previous cholecystectomy, 17% with recurrent pancreatitis). Overall EUS diagnostic yield for AP etiological diagnosis was 79% (20% lithiasis, 31% acute on chronic pancreatitis, 14% pancreatic solid or cystic lesions, 5% pancreas divisum, 5% autoimmune pancreatitis, 5% ductal abnormalities), while 21% remained idiopathic. US, CECT and MRCP, taken alone or in combination, led to AP etiological diagnosis in 16 (20%) patients; among the remaining 65 patients, 49 (75%) obtained a diagnosis at EUS, with an overall EUS diagnostic gain of 61%. Sixty-eight patients had negative US; among them, EUS allowed etiological diagnosis in 59 (87%). Sixty-three patients had a negative CECT; among them, 47 (74%) obtained diagnosis with EUS. Twenty-four had a negative MRCP; among them, 20 (83%) had EUS diagnosis. Twenty-one had negative CT + MRCP, of which 17 (81%) had EUS diagnosis, with a EUS diagnostic gain of 63%. Patients with biliary etiology and without previous cholecystectomy had higher median values of alanine aminotransferase (154 *vs* 25, $P = 0.010$), aspartate aminotransferase (95 *vs* 29, $P = 0.018$), direct bilirubin (1.2 *vs* 0.6, $P = 0.015$), gamma-glutamyl transpeptidase (180 *vs* 48, $P = 0.006$) and alkaline phosphatase (150 *vs* 72, $P = 0.015$) Chronic pancreatitis diagnosis was more frequent in patients with recurrent pancreatitis at baseline (82% *vs* 21%, $P < 0.001$). During the follow-up, AP recurred in 3 patients, one of which remained idiopathic.

CONCLUSION

EUS is a good test to define AP etiology. It showed a 63% diagnostic gain over CECT + MRCP. In suitable patients, EUS should always be performed in cases of IAP. Further prospective studies are needed.

Key Words: Endoscopic ultrasound; Idiopathic acute pancreatitis; Diagnostic gain; Computed tomography; Magnetic resonance cholangiopancreatography

Core Tip: Acute pancreatitis (AP) is a common and potentially severe disease. Imaging techniques allow an etiological diagnosis in most cases. However, about 20% of cases remain idiopathic, with negative consequences on patients' outcomes. Endoscopic ultrasound (EUS) has emerged as a valid technique for the assessment of AP etiology. We share our experience with EUS in the identification of idiopathic AP etiology, after failure of one or more cross-sectional imaging techniques. We found a superiority of EUS over the standard cross-sectional imaging techniques. We therefore suggest the use of EUS to define idiopathic AP etiology in all suitable patients.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder characterized by the abnormal activation of digestive enzymes within the pancreatic gland. AP leads to the acute injury of the pancreas and may involve remote organs and systems. AP is one of the most common causes of hospitalization in the United States and Europe[1]. In most cases (about 80%), the prognosis is rapidly favorable[2]. Nevertheless, acute necrotizing pancreatitis may develop in up to 20% of cases, and it is associated with significant rates of early organ failure (38%), need for intervention (38%) and death (15%)[3].

The most common AP etiologies are common bile duct stones and alcohol abuse, accounting for about 60%-70% of all the cases[4]. Other etiologies include functional or anatomic lesions (pancreas divisum, pancreatic duct strictures/tumors, ampullary stenosis or sphincter of Oddi dysfunction), drugs, metabolic causes (hypertriglyceridemia, hypercalcemia), autoimmune disease, mechanical injury (*e.g.*, blunt abdominal trauma, postoperative), infections, ischemia, hereditary conditions and toxins[5].

AP etiology can be found in most cases by combining cross-sectional abdominal imaging techniques, such as ultrasound (US), contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP). However, 10%-30% of AP remains idiopathic (IAP) after clinical, laboratory and imaging tests[6,7]. This is a relevant issue, as 20% of patients with IAP have recurrent episodes, and 20%-30% of them develop chronic pancreatitis[6]. In recent years, endoscopic US (EUS) has emerged as a useful tool for the etiological diagnosis of AP. A recent systematic review and meta-analysis demonstrated that EUS is able to identify a potential etiology in the majority of patients with IAP[8].

EUS has shown high diagnostic accuracy for the identification of microlithiasis missed at CECT scan or MRCP[9,10]. Moreover, in a smaller but relevant percentage of cases, EUS detected small pancreatic or ampullary lesions that were not identified at CECT or magnetic resonance imaging[11-13]. To date, few data are available about the role of EUS after failure of multiple cross-sectional imaging techniques and specifically evaluating the diagnostic gain of EUS in this setting. The present study aimed to evaluate the role of EUS in the assessment of IAP etiology when US, CECT and MRCP failed.

MATERIALS AND METHODS

Study population and data collection

We performed a retrospective, single-center study. We analyzed a database of consecutive adult patients prospectively enrolled between January 2017 and December 2020 to the Ospedale Maggiore of Cremona with a diagnosis of AP. The diagnosis of AP was made when 2 of 3 of the following criteria were met: abdominal pain consistent with pancreatitis; increased serum amylase or lipase levels, by at least 3 times the upper normal of limit; and characteristic findings on conventional radiologic methods (transabdominal US and/or CECT scan). MRCP was performed as a second-line technique after a negative US and/or CECT.

A thorough medical history and complete blood tests were collected for each patient at the clinical presentation. For final inclusion in the study analyses, the following criteria were ruled out: (1) History of alcohol or other toxic substance abuse; (2) Recent abdominal trauma; (3) Medications potentially related to AP; (4) Metabolic disorder like hypertriglyceridemia (≥ 1000 mg/dL) or hypercalcemia; (5) Clear etiology of AP identified at US, CECT or MRCP, without the need for further investigations; and (6) In the case of recurrent pancreatitis (*i.e.* ≥ 2 episodes of AP), a genetic cause was ruled out by testing for *CFTR*, *SPINK-1* and *PRSS1* mutations.

Therefore, the patients included in final analysis were those diagnosed with idiopathic acute pancreatitis (IAP), according to the American College of Gastroenterology guidelines[14].

All patients included in the study had undergone EUS after at least one US, CECT or MRCP test. Specifically, EUS was performed after a negative cross-sectional technique to investigate the AP etiology and after a positive exam to confirm a suspected diagnosis, to better characterize a lesion or to obtain biopsies.

After EUS examination, patients were followed up for at least 12 mo (median 31.5 mo, range 12-55), and recurrent episodes of acute pancreatitis were recorded.

The primary aim of the study was to evaluate the diagnostic gain of EUS in the identification of IAP etiology after failure of one or more previous cross-sectional exams. The secondary aims were: to assess the overall EUS diagnostic yield for IAP etiology; to compare the baseline clinical features with the IAP diagnosis; and to analyze the frequency and types of AP recurrence during the follow-up.

Endoscopic ultrasound

EUS examination was performed by 2 experienced operators (≥ 250 exams per year) using a linear echoendoscope (Pentax Medical EG3870UTK and EG38-J10UT), after informed consent had been obtained, with the patient in a left-side position under conscious sedation. EUS was mainly performed during admission after the acute phase of pancreatitis was clinically resolved, unless conditions such as persistent biliary obstruction required earlier evaluation. EUS was performed as an outpatient procedure in cases of mild pancreatitis with early patient discharge.

The examination was considered diagnostic with the following findings: biliary stones, criteria for chronic pancreatitis, presence of solid or cystic pancreatic lesions, pancreatobiliary duct abnormality, pancreas divisum, and features of autoimmune pancreatitis.

In detail: (1) Biliary etiology was diagnosed if stones or microlithiasis/biliary sludge were seen inside the gallbladder or the common bile duct. Biliary stones were defined as hyperechoic structures with an acoustic shadow, microlithiasis was defined as hyperechoic structures of 3 mm or less in diameter, and biliary sludge was defined as a hyperechoic material without an acoustic shadow[15]; (2) Chronic

pancreatitis was defined according to the Rosemont criteria[16]; (3) Duct abnormality was diagnosed if a long pancreatobiliary junction (> 15 mm) was identified[17]; (4) Pancreas divisum was described in the presence of a dominant dorsal duct with or without evidence of communication between the ventral and dorsal ducts, or if the main pancreatic duct could not be traced from the major papilla[18]; (5) Solid or cystic pancreatic lesions were considered as the cause of AP if obstruction of the pancreatic duct was seen at EUS examination; and (6) The diagnosis of autoimmune pancreatitis was made when parenchymal or ductal features were seen (*e.g.*, diffuse pancreas enlargement with delayed enhancement), and the International Consensus Diagnostic Criteria were met[19].

Statistical analysis

The categorical variables were described as absolute frequency and percentage. The continuous variables with normal distribution were described as mean ± SD, whereas the continuous variables without normal distribution were given as median and range. Mann-Whitney test and ^{2} or Fisher's exact tests were used to associate baseline clinical and biochemical variables with biliary pancreatitis. Diagnostic yield of EUS was calculated as the overall percentage of etiological diagnosis obtained through EUS examination. EUS diagnostic gain was calculated as the percentage of additional diagnoses obtained at EUS over the total number of patients undergoing US, CECT and/or MRCP. All the analyses were carried out by computer software IBM SPSS Statistics (release 25; IBM Corporation, United States).

RESULTS

Between March 2017 and December 2020, a total of 81 patients underwent EUS for IAP (38% female, mean age at enrollment 61 ± 18 years). Fifteen (23%) patients had previous cholecystectomy, whereas 49 (77%) had an intact gallbladder. First episode of AP was the indication of EUS in 52 (81%) patients, while 12 (19%) patients had recurrent pancreatitis (58% with one episode, 42% with 2 or more episodes). The median time interval between patient admission and EUS was 5 d (range, 2-27). All patients' demographic and clinical characteristics are summarized in Table 1.

Diagnostic yield of EUS and types of diagnosis

Overall, EUS led to an etiological diagnosis in 64 (79%) of the 81 patients. The diagnoses were as follows: 16 gallstone diseases, 25 acute on chronic pancreatitis, 4 pancreas divisum, 4 pancreatic duct anomalies, 11 solid or cystic lesions (4 pancreatic carcinomas with a maximum diameter of 15, 18, 20 and 24 mm; 2 ampullary adenomas of 8 and 13 mm; 5 branch-duct intraductal papillary mucinous neoplasms with high-risk stigmata or worrisome features) and 4 with criteria of autoimmune conditions. Example images of the main diagnosis obtained by EUS are shown in Figure 1. All patients underwent EUS and at least one exam with US, CECT and MRCP. The three cross-sectional techniques, alone or in combination, led to AP etiological diagnosis in 16 (20%) of the 81 patients. All diagnoses were confirmed at the following EUS. Among the remaining 65 patients, 49 (75%) obtained a diagnosis at EUS, with an overall EUS diagnostic gain of 61%.

US and EUS: Seventy-two (89%) patients underwent US, which allowed an etiological diagnosis in 4 (6%) cases. Among the 68 patients with a negative US, EUS allowed an etiological diagnosis in 59 (87%): 14 biliary pancreatitis, 25 acute on chronic pancreatitis, 2 pancreas divisum, 4 pancreatic duct anomalies, 10 solid or cystic lesions and 4 autoimmune conditions.

CECT and EUS: CECT scan was performed in 72 patients (89%), 9 of which (13%) resulted with an etiological diagnosis. Forty-seven (74%) out of the 63 patients with negative CECT obtained an etiological diagnosis at EUS: 10 lithiasis, 18 acute on chronic, 4 pancreas divisum, 4 duct anomalies, 9 solid/cystic lesions and 2 autoimmune pancreatitis.

MRCP and EUS: MRCP was performed in 32 patients, among which 8 (24%) obtained an etiological diagnosis. EUS allowed a diagnosis in 20 (83%) of the 24 patients with negative MRCP: 4 biliary etiology, 9 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomaly, 4 solid or cystic lesions and 1 autoimmune pancreatitis.

Diagnostic gain of EUS in cases of previous negative exams

US + CECT: A combination of US and CECT was performed in 63 patients (78%); of the 54 patients with missed diagnosis at both US and CECT, 45 (83%) received a diagnosis at EUS: 10 biliary etiology, 17 acute on chronic pancreatitis, 3 pancreas divisum, 4 pancreatic duct anomalies, 8 solid or cystic lesions and 3 autoimmune conditions. EUS diagnostic gain over US + CECT was 71%.

US + MRCP: A combination of US and MRCP was performed in 31 patients (38%); of the 23 US + MRCP missed diagnosis, 20 (87%) were identified at EUS: 4 biliary etiology, 9 acute flares on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 inflammatory-

Table 1 Demographic and clinical features of the 64 patients analyzed

Parameter	*n* = 81	EUS diagnosis, *n* = 64	Missed EUS diagnosis, *n* = 17	*P* value
Male, *n* (%)	51 (63)	43 (67)	8 (46)	0.208
Age at enrollment, mean ± SD, yr	61 ± 18	62 ± 18	59 ± 16	
Previous cholecystectomy, *n* (%)	19 (23)	18 (28)	0	0.028
Recurrent pancreatitis, *n* (%)	14 (17)	14 (22)	0	0.101
One episode, *n* (%)	7 (9)			
≥ 2 episodes, *n* (%)	6 (7)			
Amylase, median (range)	468 (107-4988)	465 (123-4988)	500 (107-4753)	0.861
Lipase, median (range)	777 (87-23840)	774 (87-23840)	780 (96-12800)	0.914
Gamma-glutamyl transpeptidase, median (range)	70 (9-1665)	70 (9-1665)	125 (11-640)	0.707
Alkaline phosphatase, median (range)	78 (32877)	78 (32-877)	90 (32-185)	0.707
Direct bilirubin, median (range)	0.7 (0.2-8.5)	0.4 (0.2-3)	0.7 (0.2-8.5)	0.933
Alanine aminotransferase, median (range)	34 (6-793)	34 (6-793)	33 (7-596)	0.488
Aspartate aminotransferase, median (range)	38 (11-704)	34 (11-704)	33 (15-301)	0.732
Abdominal US, *n* (%)	72 (89)	63 (98)	9 (54)	< 0.001
Abdominal CECT, *n* (%)	72 (89)	56 (88)	16 (94)	1.000
MRCP, *n* (%)	32 (39)	28 (44)	4 (24)	0.220
EUS findings, *n* (%)		NA	NA	NA
Normal (final IAP diagnosis)	17 (21)			
Biliary	16 (20)			
Microlithiasis / biliary sludge	9 (11)			
Acute on chronic pancreatitis	25 (31)			
Solid or cystic lesions	11 (14)			
Pancreatic adenocarcinoma	4 (5)			
Ampullary adenoma	2 (3)			
BD-IPMN with high-risk stigmata or worrisome features	5 (6)			
Pancreas divisum	4 (5)			
Ductal anomaly	4 (5)			
Autoimmune criteria	4 (5)			

BD-IPMN: Branch-duct intraductal papillary mucinous neoplasms; CECT: Contrast enhanced computed tomography; IAP: Idiopathic acute pancreatitis; MRCP: Magnetic resonance cholangiopancreatography; SD: Standard deviation; US: Ultrasound; EUS: Endoscopic ultrasound; NA: Not available.

autoimmune condition. EUS diagnostic gain over US + MRCP was 65%.

CECT + MRCP: CECT and MRCP were both performed in 27 patients; of the 21 CECT + MRCP missed diagnoses, 17 (81%) were identified at EUS: 3 gallstone disease, 7 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 autoimmune condition. EUS diagnostic gain over CECT + MRCP was 63%.

US + CECT + MRCP: Finally, 25 patients (31%) received all 3 cross-sectional techniques, without obtaining the AP etiological diagnosis in 19 cases; among them, EUS allowed a diagnosis in 17 (89%) cases: 3 gallstone disease, 7 acute on chronic pancreatitis, 1 pancreas divisum, 1 pancreatic duct anomalies, 4 solid or cystic lesions and 1 autoimmune condition. EUS diagnostic gain over US + CECT + MRCP was 68%.

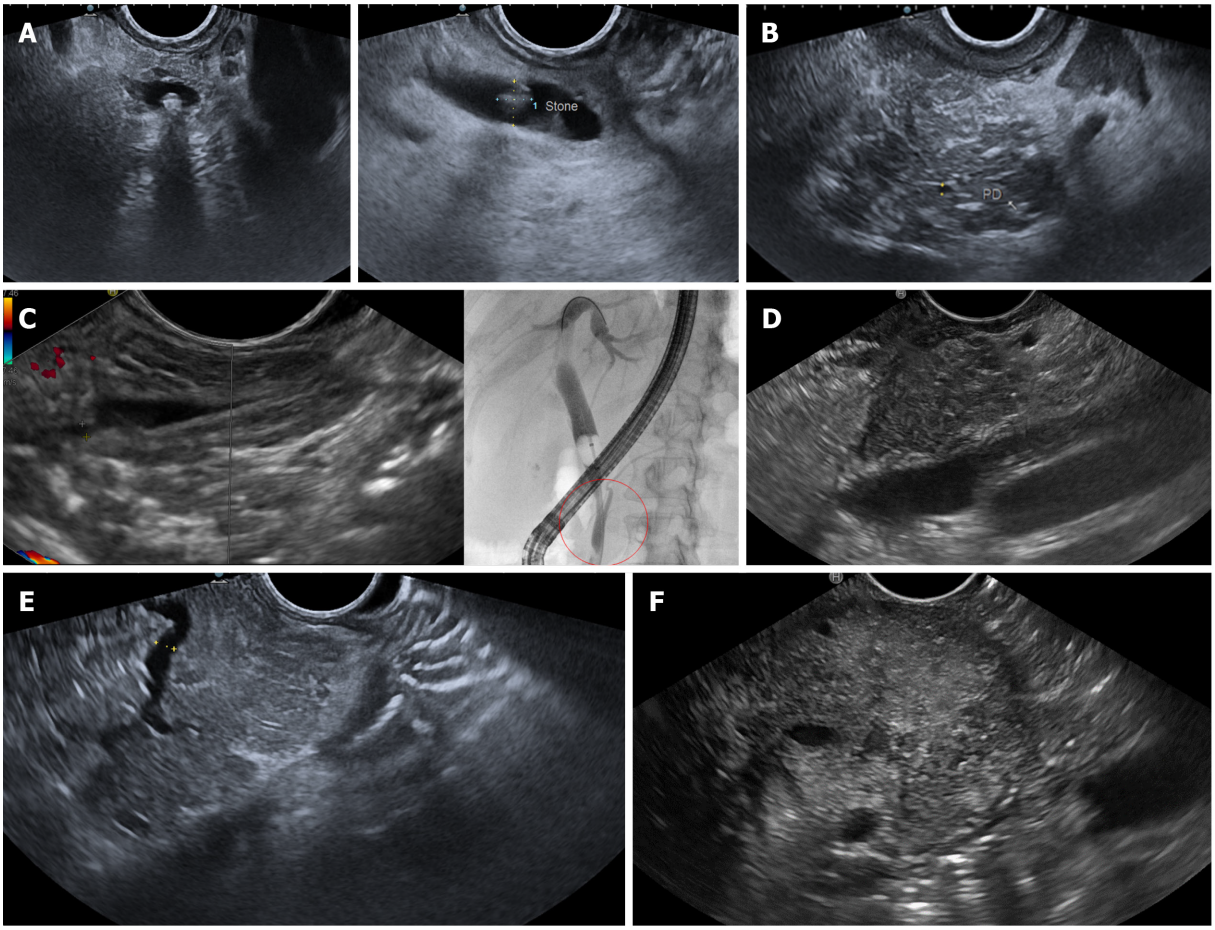

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Figure 1 Illustrative images of the main etiological diagnoses of acute pancreatitis obtained by endoscopic ultrasound. A: Choledocholithiasis: endoscopic ultrasound (EUS) images of a small (3-4 mm) shadowing stone located in the distal common bile duct, obtained from the bulb (on the left) and descending duodenum (on the right) stations; B: Early chronic pancreatitis: EUS image showed a lobular pancreatic parenchyma with hyperechoic strands and foci, with hyperechoic margins of the Wirsung's duct, all of which are minor criteria for chronic pancreatitis; C: Anomalous pancreaticobiliary junction: EUS image from the descending duodenum showed the confluence of Wirsung's duct and common bile duct into a long (15 mm) common channel (on the left). The anomaly was then confirmed by retrograde cholangiopancreatography (on the right), also showing lithiasis of the distal part of the common channel; D: Pancreatic lesion: EUS image of a small (15 mm) solid lesion located in the pancreatic head; the lesion appeared hypoechoic and with irregular / infiltrating margins and comes close to the portal venous confluence. Histology confirmed a pancreatic adenocarcinoma; E: Pancreas divisum: EUS image from the descending duodenum showed a dominant dorsal pancreatic duct (PD), draining in the minor papilla; F: Autoimmune pancreatitis: EUS image showed a diffuse hypoechoic pancreatic enlargement, with hypoechoic parenchymal margins, at the level of the body (clearly visible the splenic vessels on the left). After contrast enhancement, the pancreas showed homogeneous early hypervascularization. Histology obtained by fine-needle biopsy revealed inflammatory infiltrates, excluding cancer.

The percentage of types of EUS diagnosis after the different exam combinations are shown in Table 2.

Correlation between IAP diagnosis and clinical parameters

All patients without etiological diagnosis at EUS had no previous cholecystectomy compared to 28% with EUS diagnosis ($P = 0.028$). Patients with a final diagnosis of biliary pancreatitis had higher baseline median values of alanine aminotransferase (median value 154 *vs* 25, $P = 0.010$), aspartate aminotransferase (median value 95 *vs* 29, $P = 0.018$), direct bilirubin (median value 1.2 *vs* 0.6, $P = 0.015$), gamma-glutamyl transpeptidase (median value 180 *vs* 48, $P = 0.006$) and alkaline phosphatase (median value 150 *vs* 72, $P = 0.015$) compared to patients with non-biliary diagnosis. After differentiating between patients with or without previous cholecystectomy, these associations were maintained only for the non-cholecystectomy group. Noteworthy, when differentiating between first-episode and recurrent pancreatitis, chronic pancreatitis was the diagnosis at EUS in 21% and 82% of cases, respectively, a difference that was statistically significant ($P < 0.001$).

Etiology-based therapeutic intervention and follow-up data

During the follow-up, 12 out of the 16 patients diagnosed with biliary pancreatitis had evidence of choledocholithiasis; all of them underwent successful stone removal by endoscopic retrograde cholangiopancreatography (ERCP). Five out of the 25 patients with chronic pancreatitis underwent ERCP with pancreatic sphincterotomy (5/5) and pancreatic duct stenting (2/5) because of the evidence of

Table 2 Frequencies of acute pancreatitis etiologies at endoscopic ultrasound according to the type of previous negative exam/s

	Type of previous negative exam/s						
Type of AP etiology at EUS	US	CECT	MRCP	US + CECT	US + MRCP	CECT + MRCP	US + CECT + MRCP
Biliary; microlithiasis/biliary sludge	20%; 10%	16%; 5%	17%; 17%	19%; 7%	18%; 18%	14%; 14%	16%; 16%
Acute on chronic	37%	29%	38%	32%	39%	33%	37%
Solid or cystic lesions	15%	14%	17%	15%	18%	19%	21%
Pancreas divisum	3%	6%	4%	5%	4%	5%	5%
Anomalous pancreaticobiliary junction	6%	6%	4%	7%	4%	5%	5%
Autoimmune criteria	6%	3%	4%	5%	4%	5%	5%
Idiopathic	13%	26%	16%	17%	3%	9%	11%

AP: Acute pancreatitis; CECT: Contrast enhanced computed tomography; EUS: Endoscopic Ultrasound; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasound.

Wirsung's duct stenosis. Among the 11 patients with solid or cystic lesions as the cause of IAP, 4 were treated surgically, while the others were evaluated for a neoadjuvant or palliative approach. The 4 patients with features of autoimmune pancreatitis began steroid therapy with a good response.

During the follow-up time, a further episode of acute pancreatitis was observed in 3 patients (3.7%). Genetic tests for *CFTR*, *SPINK-1* and *PRSS1* mutations tested negative. All patients underwent EUS at recurrence. Two of these already had an EUS diagnosis of pancreas divisum and anomalous pancreatobiliary junction that were confirmed. The other had been initially diagnosed as idiopathic pancreatitis, which remained idiopathic even after the EUS examination performed after recurrence.

DISCUSSION

Our study investigated the role of EUS in the etiological diagnosis of IAP. Overall, the diagnostic yield of EUS for the identification of AP etiology was 80%, with 20% of patients with a final IAP diagnosis, which is in line with previous literature data[20,21]. This result is in keeping with two previous published meta-analyses reporting that EUS can detect a cause in most patients with IAP[8,22]. We found a high diagnostic gain of EUS after all combinations of previous negative cross-sectional techniques; interestingly, diagnostic gain remained remarkably high even after the combination of CECT and MRCP. This result supports EUS as the technique of choice after a negative CECT if the patient is suitable for endoscopic examination, while MRCP could be reserved for patients at elevated risk for invasive procedures.

The most common etiologies identified at EUS were lithiasis, acute on chronic pancreatitis and solid or cystic lesions. All the lithiasis identified at EUS after MRCP were microlithiasis/biliary sludge of gallbladder or common bile duct compared with about half after CECT; this finding confirms the superiority of EUS over MRCP in the identification of lithiasis of small size, as reported previously[9,21-24]. An increase in transaminases is known to have a high positive predictive value for gallstone pancreatitis[25]. Interestingly, in our study, patients with biliary pancreatitis showed higher levels of liver enzymes as compared to other types of diagnosis but only in the group without previous cholecystectomy, while patients with previous cholecystectomy showed similar median values of liver enzymes. This result seems to identify patients without prior cholecystectomy and with increased transaminases as those at greatest risk of biliary pancreatitis and suggests that these patients could benefit from EUS as the first diagnostic test, eventually followed by ERCP in the same session if the diagnosis is confirmed[26-28].

Chronic pancreatitis was the most frequent diagnosis overall, with similar frequencies after all combinations of previous cross-sectional imaging techniques. This data is in line with the current evidence that EUS has the highest diagnostic performance in the identification of chronic pancreatitis features[29,30]. This is especially true in the setting of early chronic pancreatitis where thanks to the high resolution, EUS may detect subtle parenchymal and ductal changes such as irregular ductal contour, side branch ectasia ≥1 mm and parenchymal lobularity, which are minor diagnostic criteria according to the Rosemont criteria[31-34]. When differentiating between single episode or recurrent pancreatitis at baseline, diagnosis of chronic pancreatitis was much more frequent in patients with recurrent forms; this result supports the use of EUS as the first diagnostic technique for the identification of AP etiology in this subgroup of patients.

Regarding solid lesions, all pancreatic carcinomas missed at CECT were 25 mm or less in size. This data agrees with previous evidence showing a superiority of EUS over CECT for the diagnosis of small pancreatic lesions[35-38]. Interestingly, the percentage of solid lesions identified at EUS was similar in groups with or without previous MRCP, suggesting that this technique does not improve the ability to diagnose small pancreatic lesions. The identification of solid pancreatic lesions, as well as cholelithiasis or choledocholithiasis, not seen at previous examinations is of paramount importance since it significantly changes the patient management and particularly the referral to surgery or ERCP. This is especially true for small pancreatic cancers, which may be suitable for curative treatment. Most cystic lesions were instead diagnosed after US and/or CECT failure. Indeed, as already demonstrated, MRCP and EUS have comparable diagnostic accuracy for the assessment of cystic lesions[39], although EUS can better identify some high-risk or worrisome features such as enhancing mural nodules or thickened or enhancing cyst walls[40].

Pancreatic duct anomalies, including pancreas divisum and anomalous pancreaticobiliary junction, were diagnosed at EUS in about 10% of cases. This percentage was the same even after the combination of CECT and MRCP, corroborating a high sensitivity of EUS in obtaining a detailed study of the distal portion of the pancreatic duct, as already reported in the literature[41,42]. In the meta-analysis by Wan *et al*[22], EUS and MRCP were equally effective in identifying pancreas divisum, while MRCP after secretin stimulation was superior to both techniques. However, due to increased costs and practical issues, secretin-enhanced MRCP has failed to gain widespread United States use across radiology practices[43] and is not routinely performed in our center.

Incidence of further AP episodes during the follow-up was low (3%) and related to non-modifiable causes (one idiopathic form and one pancreatic duct anomaly). The endoscopic treatment of all choledocholithiasis, followed by cholecystectomy when necessary, and of chronic pancreatitis when indicated may have contributed to reducing the risk of pancreatitis recurrence.

The strengths of the study were the homogeneity of the population, the availability of detailed clinical information and the availability of a long follow-up period after the treatment approach. The main limitations were the small sample size and the retrospective nature of the study, with the need of prospective, multicentric studies in order to delineate a diagnostic algorithm that optimizes the use of EUS in AP.

CONCLUSION

In conclusion, our study supports the role of EUS as the technique of choice in IAP after failure of one or more cross-sectional techniques including CECT and MRCP. We suggest the use of EUS as the first-level technique in patients presenting with increased liver enzymes and with no previous cholecystectomy and in the setting of recurrent pancreatitis. Given its high diagnostic yield, we also propose EUS as the first-line investigation in all suitable patients presenting with IAP. Finally, larger and prospective studies investigating not only the diagnostic but also the prognostic value of EUS in IAP are needed.

ARTICLE HIGHLIGHTS

Research background

Idiopathic acute pancreatitis (IAP) is a common condition and represents a diagnostic challenge because up to 20% of patients with IAP have recurrent episodes and may evolve to chronic pancreatitis. Endoscopic ultrasound (EUS) is highly effective in the etiological diagnosis of IAP, even after failure of a previous imaging technique. A significant proportion of AP remains idiopathic even after multiple imaging techniques, mainly including abdominal US, contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP).

Research motivation

The role of EUS in IAP has been established by multiple studies, including meta-analyses. However, limited data are currently available about the diagnostic gain of EUS in cases of failure of multiple previous imaging techniques.

Research objectives

The primary aim of the study was to evaluate the diagnostic gain of EUS after failure of US, CECT and MRCP and particularly after different combination of these techniques. The secondary aims were to assess the overall EUS diagnostic yield in IAP, to associate the baseline clinical features with the specific IAP diagnosis and to analyze the frequency and types of AP recurrence during the follow-up.

Research methods

We performed a retrospective, single-center study. We enrolled all consecutive adult patients undergoing EUS for IAP over a 3-year period at the Ospedale Maggiore of Cremona. IAP was defined when a clear etiology could not be identified after a thorough medical history, complete blood tests and after performing at least one US, CECT or MRCP exam. The EUS diagnostic gain was calculated as the percentage of additional diagnoses obtained at EUS over the total number of patients undergoing US, CECT and/or MRCP.

Research results

Overall EUS diagnostic yield was 79%, with 21% of AP remaining idiopathic. This percentage is in line with the current literature. Gallstone disease and chronic pancreatitis were the most frequent diagnoses (20% and 31%, respectively). The EUS diagnostic gain over the associations of CECT + MRCP and US + CECT + MRCP was 63% and 68%, respectively. This is a relevant result that confirms the superiority of EUS in the etiological diagnosis of IAP, particularly in detecting microlithiasis and early signs of chronic pancreatitis. In patients without a previous cholecystectomy and with a final diagnosis of biliary pancreatitis, higher baseline median values of liver enzymes were found. Moreover, in patients with recurrent pancreatitis, chronic pancreatitis was the diagnosis in 82% of cases. These results suggest a high efficacy of EUS in the etiological diagnosis of IAP in patients without previous cholecystectomy and with recurrent pancreatitis. During a median follow-up of 31.5 mo, an additional episode of pancreatitis was observed in 3.7% of patients.

Research conclusions

EUS has a high diagnostic yield in IAP. About two-thirds of patients with IAP without etiological diagnosis with various combinations of US, CECT and MRCP received a diagnosis at EUS. This finding confirms the superiority of EUS over these techniques and proposes EUS as the investigation of first choice in all suitable patients. EUS shows the highest diagnostic gain in the setting of increased liver enzymes with no previous cholecystectomy and in the setting of recurrent pancreatitis.

Research perspectives

The role of EUS in the etiological diagnosis of IAP has been established by multiple studies including meta-analyses. Our study provided additional data supporting the high diagnostic gain of EUS in cases of failure of multiple previous imaging techniques. Future research should focus on the prognostic value of EUS in the setting of IAP, since patient management may change following the EUS diagnosis. Large multicentric and prospective studies addressing this issue are needed.

FOOTNOTES

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REFERENCES

1 **Petrov MS**, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 175-184 [PMID: 30482911 DOI: 10.1038/s41575-018-0087-5]

2 **Singh VK**, Bollen TL, Wu BU, Repas K, Maurer R, Yu S, Mortele KJ, Conwell DL, Banks PA. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol* 2011; **9**: 1098-1103 [PMID: 21893128 DOI: 10.1016/j.cgh.2011.08.026]

3 **van Santvoort HC**, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, Boermeester MA, van Goor H, Dejong CH, van Eijck CH, van Ramshorst B, Schaapherder AF, van der Harst E, Hofker S, Nieuwenhuijs VB, Brink MA, Kruyt PM, Manusama ER, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, Cuesta MA, Wahab PJ, Gooszen HG; Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011; **141**: 1254-1263 [PMID: 21741922 DOI: 10.1053/j.gastro.2011.06.073]

4 **Boxhoorn L**, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC, Besselink MG. Acute pancreatitis. *Lancet* 2020; **396**: 726-734 [PMID: 32891214 DOI: 10.1016/S0140-6736(20)31310-6]

5 **Guda NM**, Trikudanathan G, Freeman ML. Idiopathic recurrent acute pancreatitis. *Lancet Gastroenterol Hepatol* 2018; **3**: 720-728 [PMID: 30215363 DOI: 10.1016/S2468-1253(18)30211-5]

6 **Levy MJ**, Geenen JE. Idiopathic acute recurrent pancreatitis. *Am J Gastroenterol* 2001; **96**: 2540-2555 [PMID: 11569674 DOI: 10.1111/j.1572-0241.2001.04098.x]

7 **Steinberg W**, Tenner S. Acute pancreatitis. *N Engl J Med* 1994; **330**: 1198-1210 [PMID: 7811319 DOI: 10.1056/NEJM199404283301706]

8 **Umans DS**, Rangkuti CK, Sperna Weiland CJ, Timmerhuis HC, Bouwense SAW, Fockens P, Besselink MG, Verdonk RC, van Hooft JE; Dutch Pancreatitis Study Group. Endoscopic ultrasonography can detect a cause in the majority of patients with idiopathic acute pancreatitis: a systematic review and meta-analysis. *Endoscopy* 2020; **52**: 955-964 [PMID: 32557477 DOI: 10.1055/a-1183-3370]

9 **Kondo S**, Isayama H, Akahane M, Toda N, Sasahira N, Nakai Y, Yamamoto N, Hirano K, Komatsu Y, Tada M, Yoshida H, Kawabe T, Ohtomo K, Omata M. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed-tomographic cholangiography. *Eur J Radiol* 2005; **54**: 271-275 [PMID: 15837409 DOI: 10.1016/j.ejrad.2004.07.007]

10 **Smith I**, Ramesh J, Kyanam Kabir Baig KR, Mönkemüller K, Wilcox CM. Emerging Role of Endoscopic Ultrasound in the Diagnostic Evaluation of Idiopathic Pancreatitis. *Am J Med Sci* 2015; **350**: 229-234 [PMID: 26252794 DOI: 10.1097/MAJ.0000000000000541]

11 **Valverde-López F**, Ortega-Suazo EJ, Wilcox CM, Fernandez-Cano MC, Martínez-Cara JG, Redondo-Cerezo E. Endoscopic ultrasound as a diagnostic and predictive tool in idiopathic acute pancreatitis. *Ann Gastroenterol* 2020; **33**: 305-312 [PMID: 32382235 DOI: 10.20524/aog.2020.0464]

12 **Tepox-Padrón A**, Bernal-Mendez RA, Duarte-Medrano G, Romano-Munive AF, Mairena-Valle M, Ramírez-Luna MÁ, Marroquin-Reyes JD, Uscanga L, Chan C, Domínguez-Rosado I, Hernandez-Calleros J, Pelaez-Luna M, Tellez-Avila F. Utility of endoscopic ultrasound in idiopathic acute recurrent pancreatitis. *BMJ Open Gastroenterol* 2021; **8** [PMID: 33402380 DOI: 10.1136/bmjgast-2020-000538]

13 **Somani P**, Sunkara T, Sharma M. Role of endoscopic ultrasound in idiopathic pancreatitis. *World J Gastroenterol* 2017; **23**: 6952-6961 [PMID: 29097868 DOI: 10.3748/wjg.v23.i38.6952]

14 **Tenner S**, Baillie J, DeWitt J, Vege SS, Gastroenterology ACo. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-1415 [DOI: 10.1038/ajg.2013.218]

15 **Diehl AK**, Holleman DR Jr, Chapman JB, Schwesinger WH, Kurtin WE. Gallstone size and risk of pancreatitis. *Arch Intern Med* 1997; **157**: 1674-1678 [PMID: 9250228]

16 **Catalano MF**, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification.
Gastrointest Endosc 2009; 69: 1251-1261 [DOI: 10.1016/j.gie.2008.07.043]

17 **Vila JJ**. Endoscopic ultrasonography and idiopathic acute pancreatitis. *World J Gastrointest Endosc* 2010; **2**: 107-111 [PMID: 21160725 DOI: 10.4253/wjge.v2.i4.107]

18 **Lai R**, Freeman ML, Cass OW, Mallery S. Accurate diagnosis of pancreas divisum by linear-array endoscopic ultrasonography. *Endoscopy* 2004; **36**: 705-709 [PMID: 15280976 DOI: 10.1055/s-2004-825663]

19 **Shimosegawa T**, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L; International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352-358 [PMID: 21412117 DOI: 10.1097/MPA.0b013e3182142fd2]

20 **Norton SA**, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. *Br J Surg* 2000; **87**: 1650-1655 [PMID: 11122178 DOI: 10.1046/j.1365-2168.2000.01587.x]

21 **Vila JJ**, Vicuña M, Irisarri R, de la Higuera BG, Ruiz-Clavijo D, Rodríguez-Gutiérrez C, Urman JM, Bolado F, Jiménez FJ, Arín A. Diagnostic yield and reliability of endoscopic ultrasonography in patients with idiopathic acute pancreatitis. *Scand J Gastroenterol* 2010; **45**: 375-381 [PMID: 20034361 DOI: 10.3109/00365520903508894]

22 **Wan J**, Ouyang Y, Yu C, Yang X, Xia L, Lu N. Comparison of EUS with MRCP in idiopathic acute pancreatitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2018; **87**: 1180-1188.e9 [PMID: 29225082 DOI: 10.1016/j.gie.2017.11.028]

23 **Ortega AR**, Gómez-Rodríguez R, Romero M, Fernández-Zapardiel S, Céspedes MeM, Carrobles JM. Prospective comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the etiological diagnosis of "idiopathic" acute pancreatitis. *Pancreas* 2011; **40**: 289-294 [DOI: 10.1097/mpa.0b013e318201654a]

24 **Meeralam Y**, Al-Shammari K, Yaghoobi M. Diagnostic accuracy of EUS compared with MRCP in detecting choledocholithiasis: a meta-analysis of diagnostic test accuracy in head-to-head studies. *Gastrointest Endosc* 2017; **86**: 986-993 [PMID: 28645544 DOI: 10.1016/j.gie.2017.06.009]

25 **Whitcomb DC**. Clinical practice. Acute pancreatitis. *N Engl J Med* 2006; **354**: 2142-2150 [PMID: 16707751 DOI: 10.1056/NEJMcp054958]

26 **Vila JJ**, Kutz M, Goñi S, Ostiz M, Amorena E, Prieto C, et al Endoscopic and anesthetic feasibility of EUS and ERCP combined in a single session vs two different sessions.
World J Gastrointest Endosc 2011; 3: 57-61 [DOI: 10.4253/wjge.v3.i3.57]

27 **Benjaminov F**, Stein A, Lichtman G, Pomeranz I, Konikoff FM. Consecutive *vs* separate sessions of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) for symptomatic choledocholithiasis. *Surg Endosc* 2013; **27**: 2117-2121 [PMID: 23389062 DOI: 10.1007/s00464-012-2720-7]

28 **Fabbri C**, Polifemo AM, Luigiano C, Cennamo V, Fuccio L, Billi P, Maimone A, Ghersi S, Macchia S, Mwangemi C, Consolo P, Zirilli A, Eusebi LH, D'Imperio N. Single session *vs* separate session endoscopic ultrasonography plus endoscopic retrograde cholangiography in patients with low to moderate risk for choledocholithiasis. *J Gastroenterol Hepatol* 2009; **24**: 1107-1112 [PMID: 19638088 DOI: 10.1111/j.1440-1746.2009.05828.x]

29 **Issa Y**, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur Radiol* 2017; **27**: 3820-3844 [PMID: 28130609 DOI: 10.1007/s00330-016-4720-9]

30 **Pungpapong S**, Wallace MB, Woodward TA, Noh KW, Raimondo M. Accuracy of endoscopic ultrasonography and magnetic resonance cholangiopancreatography for the diagnosis of chronic pancreatitis: a prospective comparison study. *J Clin Gastroenterol* 2007; **41**: 88-93 [DOI: 10.1097/mcg.0b013e31802dfde6]

31 **Stevens T**, Parsi MA. Endoscopic ultrasound for the diagnosis of chronic pancreatitis. *World J Gastroenterol* 2010; **16**: 2841-2850 [DOI: 10.3748/wjg.v16.i23.2841]

32 **Takasaki Y**, Ishii S, Fujisawa T, Ushio M, Takahashi S, Yamagata W, Ito K, Suzuki A, Ochiai K, Tomishima K, Saito H, Isayama H. Endoscopic Ultrasonography Findings of Early and Suspected Early Chronic Pancreatitis. *Diagnostics (Basel)* 2020; **10** [PMID: 33261170 DOI: 10.3390/diagnostics10121018]

33 **Dominguez-Munoz JE**, Drewes AM, Lindkvist B, Ewald N, Czakó L, Rosendahl J, Löhr JM; HaPanEU/UEG Working Group. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. *Pancreatology* 2018; **18**: 847-854 [PMID: 30344091 DOI: 10.1016/j.pan.2018.09.016]

34 **Kamat R**, Gupta P, Rana S. Imaging in chronic pancreatitis: State of the art review. *Indian J Radiol Imaging* 2019; **29**: 201-210 [PMID: 31367093 DOI: 10.4103/ijri.IJRI_484_18]

35 **DeWitt J**, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med* 2004; **141**: 753-763 [PMID: 15545675 DOI: 10.7326/0003-4819-141-10-200411160-00006]

36 **Michl P**, Pauls S, Gress TM. Evidence-based diagnosis and staging of pancreatic cancer. *Best Pract Res Clin Gastroenterol* 2006; **20**: 227-251 [PMID: 16549326 DOI: 10.1016/j.bpg.2005.10.005]

37 **Yasuda K**, Mukai H, Nakajima M. Endoscopic ultrasonography diagnosis of pancreatic cancer. *Gastrointest Endosc Clin N Am* 1995; **5**: 699-712 [PMID: 8535618]

38 **Bronstein YL**, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, Broemeling LD, Cleary KR, Charnsangavej C. Detection of small pancreatic tumors with multiphasic helical CT. *AJR Am J Roentgenol* 2004; **182**: 619-623 [PMID: 14975959 DOI: 10.2214/ajr.182.3.1820619]

39 **Kim YC**, Choi JY, Chung YE, Bang S, Kim MJ, Park MS, Kim KW. Comparison of MRI and endoscopic ultrasound in the characterization of pancreatic cystic lesions. *AJR Am J Roentgenol* 2010; **195**: 947-952 [PMID: 20858823 DOI: 10.2214/AJR.09.3985]

40 **Lu X**, Zhang S, Ma C, Peng C, Lv Y, Zou X. The diagnostic value of EUS in pancreatic cystic neoplasms compared with CT and MRI. *Endosc Ultrasound* 2015; **4**: 324-329 [PMID: 26643701 DOI: 10.4103/2303-9027.170425]

41 **Shen Z**, Munker S, Zhou B, Li L, Yu C, Li Y. The Accuracies of Diagnosing Pancreas Divisum by Magnetic Resonance Cholangiopancreatography and Endoscopic Ultrasound: A Systematic Review and Meta-analysis. *Sci Rep* 2016; **6**: 35389 [PMID: 27734952 DOI: 10.1038/srep35389]

42 **Kushnir VM**, Wani SB, Fowler K, Menias C, Varma R, Narra V, et al Sensitivity of endoscopic ultrasound, multidetector computed tomography, and magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a tertiary center experience.
Pancreas 2013; 42: 436-441 [DOI: 10.1097/mpa.0b013e31826c711a]

43 **Swensson J**, Zaheer A, Conwell D, Sandrasegaran K, Manfredi R, Tirkes T. Secretin-Enhanced MRCP: How and Why-*AJR* Expert Panel Narrative Review. *AJR Am J Roentgenol* 2021; **216**: 1139-1149 [PMID: 33263419 DOI: 10.2214/AJR.20.24857]

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ORIGINAL ARTICLE

Retrospective Study

Change point analysis validation of the learning curve in laparoscopic colorectal surgery: Experience from a non-structured training setting

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Abstract

BACKGROUND

The introduction of minimal invasive principles in colorectal surgery was a major breakthrough, resulting in multiple clinical benefits, at the cost, though, of a notably steep learning process. The development of structured nation-wide training programs led to the easier completion of the learning curve; however, these programs are not yet universally available, thus prohibiting the wider adoption of laparoscopic colorectal surgery.

AIM

To display our experience in the learning curve status of laparoscopic colorectal surgery under a non-structured training setting.

METHODS

We analyzed all laparoscopic colorectal procedures performed in the 2012-2019 period under a non-structured training setting. Cumulative sum analysis and change-point analysis (CPA) were introduced.

RESULTS

Overall, 214 patients were included. In terms of operative time, CPA identified the 110th case as the first turning point. A plateau was reached after the 145th case. Subgroup analysis estimated the 58th for colon and 52nd case for rectum operations as the respective turning points. A learning curve pattern was confirmed for pathology outcomes, but not in the conversion to open surgery and morbidity endpoints.

CONCLUSION

The learning curves in our setting validate the comparability of the results, despite the absence of National or Surgical Society driven training programs.

Key Words: Colorectal; Education; Gastrointestinal; Laparoscopy; Outcomes

Core Tip: In terms of operative time, the learning curve of a dedicated colorectal surgical team consists of three phases. Change point analysis identified the 110th case as the separation key-point of the first two phases. A plateau was reached after the 145th case. Although we were able to confirm the presence of a learning curve pattern in the histopathological endpoints, this was not the case for the open conversion and morbidity outcomes. Formal training program initiatives are necessary for the safe and efficient implementation of laparoscopic colorectal operations.

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INTRODUCTION

The introduction of minimal invasive principles in colorectal surgery, during the last two decades, was a major breakthrough[1]. Multiple studies confirmed the advantages of a minimal invasive approach, including reduced analgesic requirements, fewer complications, and a shorter recovery period[2].

Nonetheless, the accrual of these benefits depends on the completion of an elongated learning process [3-5]. Due to the complexity of laparoscopic colorectal operations (LCRO) and the innate dexterity requirements, the accumulation of the respective surgical skills is quite demanding[6-9]. Thus, like other multi-leveled procedures, learning curves were universally adopted for the assessment of surgical competency[10-13].

Although there is a remarkable heterogeneity in the turning points of learning curves for LCRO, current evidence suggests that at least 100 consecutive operations are needed to obtain proficiency[14-17]. During the initial phase, an analogous variation in endpoints, such as morbidity and open conversion rates, is expected[3,18-24].

The determination of the individual elements that contribute to the elongation of the learning curve was a major step towards the establishment of a safety and training culture in laparoscopic colorectal surgery[14,23,25]. Subsequently, the development of structured nation-wide training programs expedited the completion of the respective learning curves[26-28]. Among the various components of these programs are the formation of specialized colorectal surgical groups, the conduction of hands-on courses, and the introduction of mentor guidance during the first cases[26-29]. Unfortunately, these initiatives are not yet implemented in all health systems, thus restraining the efficient dissemination of the minimal invasive principles in colorectal surgery[9,24,30].

Therefore, we designed this study to analyze the laparoscopic colorectal surgery learning curves, outside a formal national or surgical society driven training program.

MATERIALS AND METHODS

This study is a retrospective analysis of a prospectively collected database. Between January 2012 and December 2019, data from all laparoscopic colorectal resections performed by a specialized colorectal surgical team, were recorded in an institutional database. All patients, prior to their inclusion, provided informed consent for data recording, analyses, and future publication. This study report follows the STROBE guidelines[31].

The surgical team consisted of two consultant surgeons with previous experience in laparoscopic general surgery (G.T. and I.B.). Six months prior to the onset of the study, the surgeons attended both national and international specialized formal courses and performed their initial operations under proctoring. However, this learning process was not based on any national or scientific society training program, due to the absence of such initiatives in Greece. The surgical team was also supported by a dedicated pathology team responsible for the evaluation of the resected specimens.

All operations were performed with four or five trocars. Dissection was completed using an energy source. A medial to lateral approach was implemented in all patients. In case of malignancy, the appropriate oncological principles (Complete mesocolic excision/ Total mesorectal excision CME/TME and Central vascular ligation CVL) were followed. Splenic flexure mobilization was always performed in left sided tumors. A structured pathology report was also provided.

All adult patients (age > 18 years) submitted to elective or semi-elective laparoscopic colorectal surgery for benign or malignant disease were deemed as eligible. The following exclusion criteria were considered: (1) Age < 18 years; (2) American Society of Anesthesiologists (ASA) score > III; (3) Emergency surgery, *e.g.*, for peritonitis and perforation; and (4) Cases not performed by the above-mentioned surgical team.

The primary endpoint of our study was to identify the learning curve status of the operation duration in patients submitted to LCRO. Subgroup analysis for colon (LCO) and rectal operations (LRO) was also performed. Secondary endpoints included operative characteristics (complication and open conversion rates) and specimen pathology quality outcomes. Postoperative complications were any Clavien Dindo ≥ 2 adverse events. The complexity of each operation was graded on the basis of the Miskovic *et al*[23] classification system. Data extraction was completed by a group of senior researchers (I.M., G.V., and A.V.).

Statistical analysis

Prior to any statistical analysis, a Shapiro-Wilk normality test was applied to all continuous variables. Since normality was not proven, a non-parametric approach was implemented. Mann-Whitney *U* test was used for the comparison of continuous variables. Kruskal Wallis *H* test was applied in multiple comparisons of continuous data. Categorical variables were analyzed by Pearson chi square test, while proportions were evaluated by the *Z* test. Correlation was assessed through a Spearman's rank-order correlation test.

To identify variations in the changing rate of the studied variables and plot the respective learning curve (LC), cumulative sum (CUSUM) analysis was performed. CUSUM analysis was applied to all above-mentioned endpoints.

The CUSUM analysis plots that confirmed a significant LC pattern, were further evaluated by change-point analysis (CPA). CPA allows the identification of even small trend shifts and provides the respective statistical significance of each change. The CPA analysis incorporated the application of 1000 bootstraps, and a 50% confidence level (CL) for candidate changes.

The acceptable rate of missing values was < 10%. Missing data were handled using the multiple imputation technique. Continuous data are reported in the form of median (interquartile range), whereas categorical variables are provided as number (percentage). Significance was considered at the level of $P < 0.05$. Statistical analyses were completed with STATA v.13 and SPSS v.23 software.

RESULTS

Patient characteristics are summarized in Table 1. Overall, 214 LCRO were included in the study. More specifically, 76 (35.5%) right colectomies, 31 (14.5%) left colectomies, 26 (12.2%) sigmoidectomies, 72 (33.6%) low anterior resections (LAR), 7 (3.3%) ultra-LAR, and 2 (2.4%) abdominoperineal resections (APR) were performed. Most of the cases displayed a level 1 (54.2%) or 2 (38.2%) complexity. Mean operation duration was 180 and 200 min for LCO and LRO, respectively. The results of the correlation analyses are reported in Supplementary Tables. The overall complication rate was 22.9%. Negative resection margins were confirmed in 95.3% of the patients. A mesocolic and mesorectal resection plane was achieved in 86.4% and 88.8% of cases, respectively.

Figure 1 illustrates the LCRO learning curve, in terms of operation duration. A declining trend of the CUSUM plot, until the 109th case was noted, followed by an upwards shift and a maximum value at the 176th case. CPA confirmed the 110th (CL: 100%) and 145th (CL: 99%) case turning points. On the basis of these findings (Table 2), the LCRO LC was subdivided in three distinct phases (phase I: 1 to 109 operations; phase II: 110 to 144 operations; and phase III: 145 to 214 operations).

Figures 2 and 3 display the learning curve plots of LCO and LRO, correspondingly. Both LC patterns were comparable. First successive cases resulted in a gradual decrease and the reach of a minimum, followed by a consequent increment of the LC line. We confirmed that the 58th (CL: 99%) and 52nd (CL: 100%) cases were the corresponding turning points of colon and rectal resections. Hence, we identified two phases of the LCO and LRO learning curve (LCO phase I: 1 to 57 operations; LCO phase II: 58 to 133 operations; LRO phase I: 1 to 51 operations; LRO phase II: 52 to 81 operations).

Table 2 summarizes the eligible patient data and the study outcomes between the various LC phases. LCRO phase III displayed a significant improvement in the specimen length ($P < 0.001$), the resection distal margin ($P < 0.001$), and the lymph node yield ($P = 0.016$).

Subgroup analyses of the LC phases showed that surgical experience was correlated with the specimen length in both LCO and LRO ($P = 0.001$ and $P < 0.001$, respectively). However, dexterity in laparoscopic surgery increased the distal resection margin ($P < 0.001$) and number of excised lymph

Table 1 Patient characteristics

		Total	Colon operations	Rectal operations	*P* value
n		214	133	81	
Sex	Male	128 (59.8%)	78 (58.6%)	50 (61.7%)	NS
	Female	86 (40.2%)	55 (41.4%)	31 (38.3%)	
Age (yr)		70 (13)	71 (14)	68 (13)	NS
BMI (kg/m^2)		27 (5)	28 (5)	26.5 (4)	NS
ASA score	I	71 (33.2%)	35 (26.3%)	36 (44.4%)	0.021
	II	117 (54.7%)	79 (59.4%)	38 (46.9%)	
	III	26 (12.1%)	19 (14.3%)	7 (8.6%)	
Diagnosis	Malignancy	206 (96.3%)	125 (94%)	81 (100%)	NS
	Diverticulitis	6 (2.8%)	6 (4.5%)	0 (0%)	
	Volvulus	1 (0.5%)	1 (0.8%)	0 (0%)	
	Crohn's disease	1 (0.5%)	1 (0.8%)	0 (0%)	
Previous operation		17 (7.9%)	13 (9.8%)	4 (4.9%)	NS
T	1	51 (24.8%)	33 (26.4%)	18 (22.2%)	NS
	2	63 (30.6%)	39 (31.2%)	24 (29.6%)	
	3	85 (41.3%)	47 (37.6%)	38 (46.9%)	
	4	7 (3.4%)	6 (4.8%)	1 (1.2%)	
N	0	153 (74.3%)	89 (71.2%)	64 (79%)	NS
	1	42 (20.4%)	30 (24%)	12 (14.8%)	
	2	11 (5.3%)	6 (4.8%)	5 (6.2%)	
M	0	205 (99.5%)	125 (100%)	80 (98.8%)	NS
	1	1 (0.5%)	0 (0%)	1 (1.2%)	
Neoadjuvant modality		19 (9.2%)	2 (1.6%)	17 (20%)	< 0.001
Complexity level	1	116 (54.2%)	74 (55.6%)	42 (51.9%)	0.022
	2	82 (38.2%)	44 (33.1%)	38 (46.9%)	
	3	6 (2.8%)	6 (4.5%)	0 (0%)	
	4	10 (4.7%)	9 (6.8%)	1 (1.2%)	
Operation	Right colectomy	76 (35.5%)	76 (57.1%)	-	< 0.001
	Left colectomy	31 (14.5%)	31 (23.3%)	-	
	Sigmoidectomy	26 (12.1%)	26 (19.5%)	-	
	Low anterior resection	72 (33.6%)	-	72 (88.9%)	
	Ultra-low anterior resection	7 (3.3%)	-	7 (8.6%)	
	Abdominoperineal resection	2 (1%)	-	2 (2.4%)	
Emergency status	Elective	212 (99.1%)	131 (98.5%)	81 (100%)	NS
	Semi-elective	2 (0.9%)	2 (1.5%)	0 (0%)	
Laparoscopic approach	Totally laparoscopic	182 (85%)	127 (95.5%)	55 (67.9%)	< 0.001
	Laparoscopy assisted	32 (15%)	6 (4.5%)	26 (32.1%)	
Preoperative optimization	Bowel preparation	191 (89.3%)	112 (84.2%)	79 (97.5%)	0.002
	Antibiotic preparation	206 (96.3%)	127 (95.5%)	79 (97.5%)	NS
	Tattoo	51 (23.8%)	28 (21.1%)	23 (28.4%)	NS
Extraction site	Pfannenstiel	95 (44.4%)	40 (30.1%)	55 (67.9%)	< 0.001

	Subumbilical	19 (8.9%)	4 (3%)	15 (18.5%)	
	Transumbilical	100 (46.7%)	89 (66.9%)	11 (13.6%)	
Anastomosis	Stapled	159 (75%)	80 (60.2%)	79 (100%)	< 0.001
	Handsewn	53 (25%)	53 (39.8%)	0 (0%)	
	Intracorporeal	112 (52.8%)	50 (37.6%)	62 (78.4%)	< 0.001
	Extracorporeal	100 (47.1%)	83 (62.4%)	17 (21.5%)	
	Protective stoma	66 (30.8%)	9 (6.8%)	57 (70.4%)	< 0.001
Operation duration (min)		180 (51)	180 (50)	200 (60)	< 0.001
Open conversion		20 (9.3%)	6 (4.5%)	14 (17.3%)	0.002
Transfusion		8 (3.7%)	4 (3%)	4 (4.9%)	NS
Tumor diameter (cm)		3 (2.2)	3 (2)	3.75 (2.5)	NS
Specimen length (cm)		20 (9)	21 (7)	15 (7)	< 0.001
Distal margin (cm)		5 (4.35)	5.25 (3.5)	4.5 (4.25)	0.01
Lymph nodes		17 (12)	19 (13)	15 (11)	0.004
Lymph node ratio		0 (2.3)	0 (4)	0 (0)	NS
Histological grade	1	40 (19.4%)	20 (16%)	20 (24.7%)	NS
	2	135 (65.5%)	89 (71.2%)	46 (56.8%)	
	3	31 (15%)	16 (12.8%)	15 (18.5%)	
R status	0	204 (95.3%)	124 (99.2%)	80 (98.8%)	NS
	1	2 (0.9%)	1 (0.8%)	1 (1.2%)	
Resection plane	Mesocolic/mesorectal	183 (88.8%)	108 (86.4%)	75 (88.8%)	NS
	Intramesocolic/intramesorectal	19 (9.2%)	14 (11.2%)	5 (6.2%)	
	Muscularis propria	4 (1.9%)	3 (2.4%)	1 (1.2%)	
Extramural vascular invasion		54 (26.2%)	33 (26.4%)	21 (25.9%)	NS
Perineural invasion		21 (10.2%)	13 (10.4%)	8 (9.9%)	NS
Mucous	Focal	29 (14.1%)	20 (16%)	9 (11.1%)	NS
	Diffuse	20 (9.7%)	15 (12%)	5 (6.2%)	
Complications	Total	49 (22.9%)	33 (24.8%)	16 (19.8%)	NS
	Wound infection	9 (4.2%)	5 (3.8%)	4 (4.9%)	NS
	Wound dehiscence	2 (0.9%)	2 (1.5%)	0 (0%)	
	Leak	14 (6.5%)	10 (7.5%)	4 (4.9%)	
	Postoperative ileus	11 (5.1%)	8 (6%)	3 (3.7%)	
	Urinary tract infection	2 (0.9%)	0 (0%)	2 (2.5%)	
	Urinary retention	2 (0.9%)	1 (0.8%)	1 (1.2%)	
	Bleeding	3 (1.4%)	1 (0.8%)	2 (2.5%)	
	Pulmonary embolism	2 (0.9%)	2 (1.5%)	0 (0%)	
	ARDS	1 (0.5%)	0 (0%)	1 (1.2%)	
	Other	4 (1.9%)	4 (3%)	0 (0%)	
Relaparotomy		11 (5.1%)	8 (6%)	3 (3.7%)	NS
ICU		8 (3.7%)	5 (3.8%)	3 (3.7%)	NS
Mortality		5 (2.3%)	4 (3%)	1 (1.2%)	NS
Length of hospital stay (d)		6 (2)	6 (2)	6 (2)	NS
Follow-up (mo)		2 (3.75)	2 (5.8)	2 (2.5)	NS

NS: Non-significant; BMI: Body mass index; ASA: American Society of Anesthesiologists; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

nodes (P = 0.002) only in LCO.

Postoperative complication analysis (Supplementary Figures) in LCRO (P = 0.48), LCO (P = 0.419), and LRO (P = 0.521) did not identify an LC pattern. Similarly, open conversion was not associated with a learning curve pattern in any of the study subgroups (P = 0.3, P = 0.8, and P = 0.19, correspondingly).

Finally, the diagrams of the pathology endpoints are provided in Supplementary Figures. The 64th case (CL: 100%) was estimated as the turning point of the specimen length in colon resections. A plateau was reached after the 99th case (CL: 94%). The respective turning point of the LRO was the 47th case. There were no significant CPA turning points in the resected lymph node yield.

DISCUSSION

LC is defined as the schematic depiction of the fluctuation of an efficiency outcome, plotted over a successive number of repetitions[27,29]. Among the various statistical methodologies that have been employed for the LC evaluation are the group splitting, moving average, and CUSUM analysis[3,17,32,33]. Following an introductory learning phase, the trainee is gradually performing operations of higher complexity and difficulty[34,35]. Finally, once the iteration of the process does not affect the measured variable, mastery is achieved[16,17,32]. As a result, estimation of the LC turning points is of paramount importance in trend analysis[26].

The inherent divergence of the learning efficiency, alongside the discrepancy in the estimated LC endpoints, resulted in a significant heterogeneity in the published LC outcomes[4,36]. To be more specific, recent studies in laparoscopic colorectal surgery suggested that LC turning points fluctuate between 10[32] and 200 cases[37].

Operation duration has been frequently introduced as the LCRO LC estimated variable[27,29,32]. Nonetheless, surgical expertise assessment, based solely upon operation duration, may result in biased conclusions[27,29]. This is due to the fact that the overlapping surgical skills and the efficient collaboration between the assisting theater personnel can also impact the duration of a procedure[27,38,39]. Initial studies suggested that 23 operations may suffice for the standardization of operative time[9,24]; however, this was not validated in subsequent trials, where a 96-case margin was reported[23]. Our results estimated the first LC cut-off point at the 110th case, which is in parallel with the previous evidence.

Interestingly, we identified lower LC turning points during the individual assessment of both colon and rectal operations (LCO: 58 cases; LRO: 52 cases). This discrepancy may be the result of the combination of the two study subgroups. In particular, the estimated LC of a specific operation subtype is usually shorter, since it incorporates fewer surgical steps. Despite the fact that previous surgical competence, in either LCO or LRO, may accelerate the transposition of skills to the other, completion of LCRO LC prerequisites the attainment of mastery in both operations. Therefore, LCRO LC is equal to the summation of the two subgroup CUSUM plots.

The narrow working space, the lack of three-dimensional vision, and the fixed port positions further enhance the LCRO surgical complexity and the risk of critical intraoperative events[29]. Consequently, the learning curve status mat have a direct impact on perioperative morbidity[7,17,22,23]. Previous reports estimated that a plateau in LCRO complication rate is achieved after 140 to 200 operations[23,37]. However, we were not able to validate a LC pattern in perioperative morbidity. Similarly, MacKenzie *et al*[4] suggested the absence of fluctuation in the perioperative complications rate during the LC period. Nonetheless, these results may be due to an inadequate sample size, since larger cohorts confirmed the presence of an LC pattern in perioperative morbidity[7,17,22,23,37].

Open conversion is considered in the case of a critical event that is not amendable by the ongoing approach[17,19,32]. Typical examples include an intraoperative complication or the compromise of the oncological principles[15,19,24,25]. Although not widely accepted, conversion turning point is estimated at 61 successive operations[18,26,40]. A structured training program, though, may further reduce the above-mentioned LC margin[18,26,40]. Even though our results were in accordance with previously published reports[23], we did not confirm the presence of an LC trend in the open conversion rate.

Specimen-related endpoints are of paramount importance when evaluating the oncological efficacy of an operation[6,14,36]; lymph node yield is the most prominent among them[6,14,36]. However, this can be misleading since lymph node harvest can be affected by anthropometric and disease-related characteristics[41]. Despite these, we confirmed the presence of a significant LC trend in the number of the resected lymph nodes. Additionally, CPA validated the increase of the specimen length after the 64th LCO and 47th LRO case, respectively. We did not introduce positive resection margin and non-CME/TME dissection plane as an LC outcome, due to the scarcity of these events. Moreover, in case of CME/ TME violation, an open conversion was performed to secure adherence to oncological principles.

Table 2 Patient characteristics in different phases of the learning curve

		Overall				Colon			Rectal		
		Phase I (1-109)	Phase II (110-144)	Phase III (145-214)	*P* value	Phase I (1-57)	Phase II (58-133)	*P* value	Phase I (1-51)	Phase II (52-81)	*P* value
N		109	35	70		57	76		51	30	
Sex	Male	68 (62.4%)	24 (68.6%)	36 (51.4%)	NS	37 (64.9%)	41 (53.9%)	NS	30 (58.8%)	20 (66.7%)	NS
	Female	41 (37.6%)	11 (31.4%)	34 (48.6%)		20 (35.1%)	35 (46.1%)		21 (41.2%)	10 (33.3%)	
Age (yr)		71.5 (12)	70 (13)	69.5 (14)	NS	72 (14)	71 (13)	NS	69.5 (12)	67 (16)	NS
BMI (kg/m^2)		27 (5)	28 (4)	27 (5)	NS	28 (6)	28 (5)	NS	26 (3)	27.5 (6)	NS
ASA score	I	36 (33%)	13 (37.1%)	22 (31.4%)	NS	14 (24.6%)	21 (27.6%)	NS	21 (41.2%)	15 (50%)	NS
	II	62 (56.9%)	16 (45.7%)	39 (55.7%)		35 (61.4%)	44 (57.9%)		27 (52.9%)	11 (36.7%)	
	III	11 (10.1%)	6 (17.1%)	9 (12.9%)		8 (14%)	11 (14.5%)		3 (5.9%)	4 (13.3%)	
Diagnosis	Malignancy	106 (97.2%)	34 (97.1%)	66 (94.3%)	NS	54 (94.7%)	71 (93.4%)	NS	51 (100%)	30 (100%)	-
	Diverticulitis	2 (1.8%)	1 (2.9%)	3 (4.3%)		2 (3.5%)	4 (5.3%)		-	-	
	Volvulus	1 (0.9%)	0 (0%)	0 (0%)		1 (1.8%)	0 (0%)		-	-	
	Crohn's disease	0 (0%)	0 (0%)	1 (1.4%)		0 (0%)	1 (1.3%)		-	-	
Previous operation		13 (11.9%)	2 (5.7%)	2 (2.9%)	NS	9 (15.8%)	4 (5.3%)	0.04	4 (7.8%)	0 (0%)	NS
T	1	24 (22.6%)	6 (17.6%)	21 (31.8%)	NS	12 (22.6%)	21 (29.2%)	NS	12 (23.5%)	6 (20%)	NS
	2	34 (32.1%)	7 ((20.6%)	22 (33.3%)		16 (30.2%)	23 (31.9%)		18 (35.3%)	6 (20%)	
	3	43 (40.6%)	20 (58.8%)	22 (33.3%)		21 (39.6%)	26 (36.1%)		20 (39.2%)	18 (60%)	
	4	5 (4.7%)	1 (2.9%)	1 (1.5%)		4 (7.5%)	2 (2.8%)		1 (2%)	0 (0%)	
N	0	77 (74.5%)	25 (73.5%)	49 (74.2%)	NS	36 (67.9%)	53 (73.6%)	NS	41 (80.4%)	23 (76.7%)	NS
	1	23 (21.7%)	6 (17.6%)	13 (19.7%)		16 (30.2%)	14 (19.4%)		6 (13.7%)	5 (16.7%)	
	2	4 (3.8%)	3 (8.8%)	4 (6.1%)		1 (1.9%)	5 (6.9%)		3 (5.9%)	2 (6.7%)	
M	0	106 (100%)	34 (100%)	65 (98.5%)	NS	53 (100%)	72 (100%)	-	51 (100%)	29 (96.7%)	NS
	1	0 (0%)	0 (0%)	1 (1.5%)		-	-		0 (0%)	1 (3.3%)	
Neoadjuvant modality		6 (5.5%)	5 (14.3%)	8 (11.4%)	NS	0 (0%)	2 (2.6%)	NS	6 (11.8%)	11 (36.7%)	0.008
Complexity level	1	50 (54.1%)	13 (37.1%)	44 (62.9%)	NS	29 (50.9%)	45 (59.2%)	NS	30 (58.8%)	12 (40%)	NS
	2	42 (38.5%)	20 (57.1%)	20 (28.6%)		21 (36.8%)	23 (30.3%)		20 (39.2%)	18 (60%)	

	3	2 (1.8%)	1 (2.9%)	3 (4.3%)		2 (3.5%)	4 (5.3%)		0 (0%)	0 (0%)	
	4	6 (5.5%)	1 (2.9%)	3 (4.3%)		5 (8.8%)	4 (5.3%)		1 (2%)	0 (0%)	
Operation	Right colectomy	34 (31.2%)	13 (37.1%)	29 (41.4%)	NS	34 (59.6%)	42 (55.3%)	NS	-	-	NS
	Left colectomy	10 (9.2%)	6 (17.1%)	15 (21.4%)		10 (17.5%)	21 (27.6%)		-	-	
	Sigmoidectomy	13 (11.9%)	2 (5.7%)	11 (15.7%)		13 (22.8%)	13 (17.1%)		-	-	
	Low anterior resection	46 (42.2%)	13 (37.1%)	13 (18.6%)		-	-		45 (88.2%)	27 (90%)	
	Ultra-low anterior resection	4 (3.7%)	1 (2.9%)	2 (2.9%)		-	-		4 (7.8%)	3 (10%)	
	Abdominoperineal resection	2 (1.8%)	0 (0%)	0 (0%)		-	-		2 (4%)	0 (0%)	
Emergency status	Elective	109 (100%)	35 (100%)	68 (97.1%)	NS	57 (100%)	74 (97.4%)	NS	51 (100%)	30 (100%)	-
	Semi-elective	0 (0%)	0 (0%)	2 (2.9%)		0 (0%)	2 (2.6%)		-	-	
Laparoscopic approach	Totally laparoscopic	98 (89.9%)	24 (68.6%)	60 (85.7%)	0.009	56 (98.2%)	71 (93.4%)	NS	41 (80.4%)	14 (46.7%)	0.002
	Laparoscopy assisted	11 (10.1%)	11 (31.4%)	10 (14.3%)		1 (1.8%)	5 (6.6%)		10 (19.6%)	16 (53.3%)	
Preoperative optimization	Bowel preparation	107 (98.2%)	30 (85.7%)	54 (77.1%)	< 0.001	56 (98.2%)	56 (73.7%)	< 0.001	50 (98%)	29 (96.7%)	NS
	Antibiotic preparation	105 (96.3%)	33 (94.3%)	68 (97.1%)	NS	54 (94.7%)	73 (96.1%)	NS	50 (98%)	29 (96.7%)	NS
	Tattoo	36 (33%)	2 (5.7%)	13 (18.6%)	0.002	17 (29.8%)	11 (14.5%)	0.032	19 (37.3%)	4 (13.3%)	0.021
Extraction site	Pfannenstiel	52 (47.7%)	15 (42.9%)	28 (40%)	NS	15 (26.3%)	25 (32.9%)	NS	37 (72.5)	18 (60%)	NS
	Subumbilical	12 (11%)	4 (11.4%)	3 (4.3%)		2 (3.5%)	2 (2.6%)		9 (17.6%)	6 (20%)	
	Transumbilical	45 (41.3%)	16 (45.7%)	39 (55.7%)		40 (70.2%)	49 (64.5%)		5 (9.8%)	6 (20%)	
Anastomosis	Stapled	85 (78.7%)	24 (70.6%)	50 (71.4%)	NS	34 (59.6%)	46 (60.5%)	NS	50 (100%)	29 (100%)	NS
	Handsewn	23 (21.3%)	10 (29.4%)	20 (28.6%)		23 (40.4%)	30 (39.5%)		0 (0%)	0 (0%)	
	Intracorporeal	57 (52.8%)	16 (47.1%)	39 (55.7%)	NS	18 (31.6%)	32 (42.1%)	NS	38 (76%)	24 (82.8%)	NS
	Extracorporeal	51 (47.2%)	18 (52.9%)	31 (44.3%)		39 (68.4%)	44 (57.9%)		12 (24%)	5 (17.2%)	
	Protective stoma	38 (34.9%)	11 (31.4%)	17 (24.3%)	NS	3 (5.3%)	6 (7.9%)	NS	34 (66.7%)	23 (76.7%)	NS
Operation duration (min)		180 (50)	220 (60)	180 (40)	< 0.001	160 (48)	180 (40)	0.003	200 (50)	220 (63)	0.003
Open conversion		13 (11.9%)	2 (5.7%)	5 (7.1%)	NS	4 (7%)	2 (2.6%)	NS	8 (15.7%)	6 (20%)	NS
Transfusion		5 (4.6%)	0 (0%)	3 (4.3%)	NS	3 (5.3%)	1 (1.3%)	NS	1 (2%)	3 (10%)	NS
Tumor diameter (cm)		3 (2.1)	4 (2.4)	3 (2)	NS	3 (1.5)	3.5 (2)	NS	4 (2.4)	3 (3)	NS
Specimen length (cm)		16.25 (7.25)	22.5 (6.5)	24 (8)	< 0.001	20.5 (8)	23 (8.75)	0.001	14.25 (3.75)	21 (6)	< 0.001

Distal margin (cm)		4 (3.5)	7 (2)	7 (5)	< 0.001	4 (2.5)	7 (3.5)	< 0.001	4 (4.25)	5 (4.5)	NS
Lymph nodes		15 (10)	20 (19)	21 (12)	0.016	15 (10)	22 (13)	0.002	15 (10)	12.5 (15)	NS
Lymph node ratio		0 (0)	0 (0.8)	0 (8)	NS	0 (4.5)	0 (3.8)	NS	0 (0)	0 (13.5)	NS
Histological grade	1	26 (24.5%)	1 (2.9%)	13 (19.7%)	0.013	10 (18.9%)	10 (13.9%)	0.009	16 (31.4%)	4 (13.3%)	NS
	2	60 (56.6%)	27 (79.5%)	48 (72.7%)		31 (58.5%)	58 (80.6%)		27 (52.9%)	19 (63.3%)	
	3	20 (18.9%)	6 (17.6%)	5 (7.6%)		12 (22.6%)	4 (5.6%)		8 (15.7%)_	7 (23.3%)	
R status	0	105 (99.1%)	33 (97.1%)	66 (100%)	NS	53 (98.1%)	71 (100%)	NS	51 (100%)	29 (96.7%)	NS
	1	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.9%)	0 (0%)		0 (0%)	1 (3.3%)	
Resection plane	Mesocoli/mesorectal	91 (85.8%)	31 (91.2%)	61 (92.4%)	NS	43 (79.6%)	65 (91.5%)	NS	47 (92.2%)	28 (93.3%)	NS
	Intramesocolic/intramesorectal	12 (11.3%)	3 (8.8%)	4 (6.1%)		9 (16.7%)	5 (7%)		3 (5.9%)	2 (6.7%)	
	Muscularis propria	3 (2.8%)	0 (0%)	1 (1.5%)		2 (3.7%)	1 (1.4%)		1 (2%)	0 (0%)	
Extramural vascular invasion		30 (28.3%)	7 (20.6%)	17 (25.8%)	NS	13 (24.5%)	20 (27.8%)	NS	16 (31.4%)	5 (16.7%)	NS
Perineural invasion		13 (12.3%)	4 (11.8%)	4 (6.1%)	NS	7 (13.2%)	6 (8.3%)	NS	6 (11.8%)	2 (6.7%)	NS
Mucous	Focal	11 (10.4%)	12 (35.3%)	6 (9.1%)	0.006	6 (11.3%)	14 (19.4%)	NS	4 (7.8%)	5 (16.7%)	NS
	Diffuse	9 (8.5%)	3 (8.8%)	8 (12.1%)		7 (13.2%)	8 (11.1%)		2 (3.9%)	3 (10%)	
Complications	Total	28 (25.7%)	9 (25.7%)	12 (17.1%)	NS	15 (26.3%)	18 (23.7%)	NS	12 (23.5%)	4 (13.3%)	NS
	Wound infection	5 (4.6%)	2 (5.7%)	2 (2.9%)	NS	1 (1.8%)	4 (5.3%)	NS	4 (7.8%)	0 (0%)	NS
	Wound dehiscence	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.8%)	1 (1.3%)		0 (0%)	0 (0%)	
	Leak	8 (7.3%)	4 (11.4%)	2 (2.9%)		5 (8.8%)	5 (6.6%)		2 (3.9%)	2 (6.7%)	
	Postoperative ileus	7 (6.4%)	1 (2.9%)	3 (4.3%)		4 (7%)	4 (5.3%)		3 (5.9%)	0 (0%)	
	Urinary tract infection	2 (1.8%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)		2 (3.9%)	0 (0%)	
	Urinary retention	1 (0.9%)	0 (0%)	1 (1.4%)		0 (0%)	1 (1.3%)		1 (2%)	0 (0%)	
	Bleeding	1 (0.9%)	0 (0%)	2 (2.9%)		0 (0%)	1 (1.3%)		1 (2%)	1 (3.3%)	
	Pulmonary embolism	1 (0.9%)	1 (2.9%)	0 (0%)		1 (1.8%)	1 (1.3%)		0 (0%)	0 (0%)	
	ARDS	0 (0%)	0 (0%)	1 (1.4%)		0 (0%)	0 (0%)		0 (0%)	1 (3.3%)	
	Other	3 (2.8%)	0 (0%)	1 (1.4%)		3 (5.3%)	1 (1.3%)		0 (0%)	0 (0%)	
Relaparotomy		5 (4.6%)	3 (8.6%)	3 (4.3%)	NS	2 (3.5%)	6 (7.9%)	NS	2 (3.9%)	1 (3.3%)	NS
ICU		6 (5.5%)	1 (2.9%)	1 (1.4%)	NS	4 (7%)	1 (1.3%)	NS	2 (3.9%)	1 (3.3%)	NS

Mortality	4 (3.7%)	1 (2.9%)	0 (0%)	NS	3 (5.3%)	1 (1.3%)	NS	1 (2%)	0 (0%)	NS
Length of hospital stay (d)	6 (2)	6 (3)	6 (2)	NS	6 (2)	6 (2)	NS	6 (2)	5 (1)	NS
Follow-up (mo)	2 (3.25)	0.65 (0)	6 (5)	NS	2 (3.3)	6.8 (4.4)	NS	2 (3)	0.27 (0)	0.032

BMI: Body mass index; ASA: American Society of Anesthesiologists; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

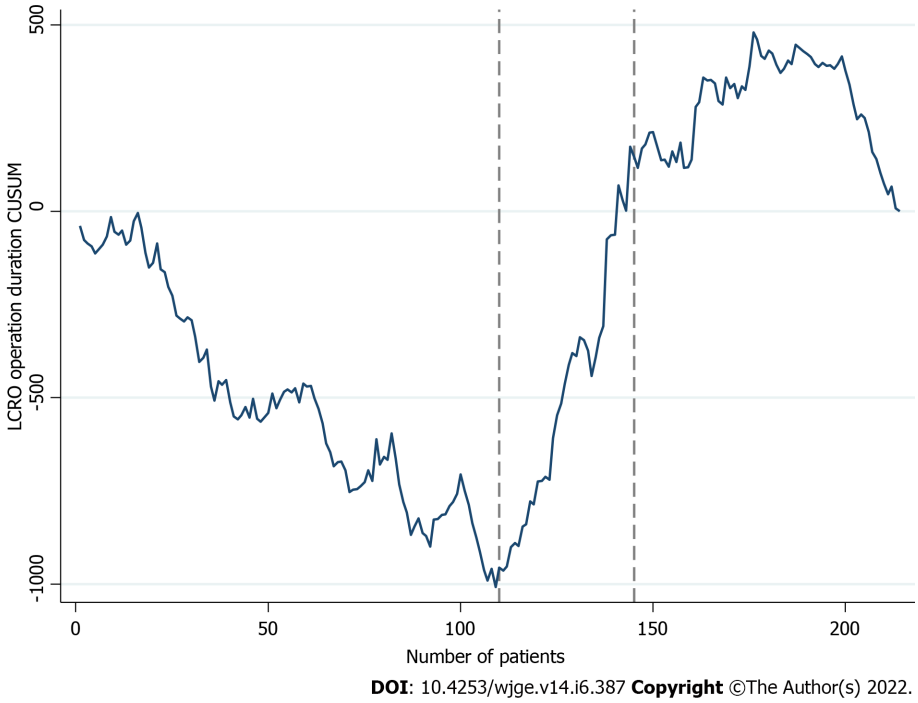
A swift completion of the learning curve is needed, in order to capitalize on the LCRO advantages [29]. Modular training enables the partitioning of the procedure in successive steps, each with its own optimization requirements[18]. The introduction of advanced LCRO courses, mentor guidance, and large operational volume exposure result in a considerable downgrade of the LC cut-off points[18,27]. These methods have been successfully enrolled in multiple national structured training programs, with promising results[17,26]. Nonetheless, surgeons in healthcare systems that have not included LCRO in their official guidelines, do not have access to similar training modules[22]. Therefore, the implementation of LCRO in such settings is based on the individual training efforts of the involved surgeons, with questionable, though, results.

In this study, we analyzed the pooled learning curve of two senior colorectal surgeons. LCRO training was not structured and included course attendance and proctor guidance. Despite this, previous experience in laparoscopic surgery and open colorectal resections could have impacted the pooled LCRO LC turning points. Therefore, our results may not reflect the typical LC pattern of an average surgical trainee.

Several limitations should be acknowledged, prior to the appraisal of our findings. First, despite the statistical significance of several LC turning points, our study incorporated a relatively small sample size. This prohibited further explanatory analyses, including risk-adjustment of the learning curves. Moreover, the innate discrepancy in terms of patient and surgical characteristics, degraded the significance of our results. Furthermore, another major source of bias could be the retrospective design of our study. Finally, the fact that only two consultants were included in this study, prohibited the safe extrapolation of these findings to a wider pool of colorectal surgeons and surgical trainees.

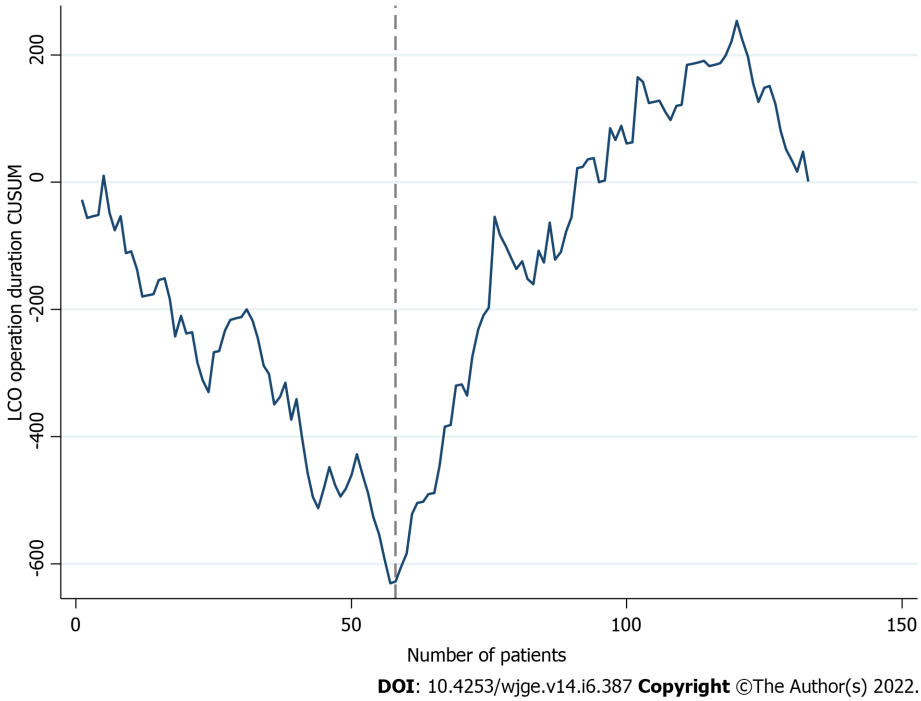
CONCLUSION

Overall, our study reported that the LCRO operation duration learning curve consists of three distinct phases. CPA estimated that the 110th case is the cut-off point between the first two phases. Stabilization of operative time is achieved after the 145th case. LCO and LRO subgroup analysis estimated the 58th and 52nd case as the respective turning points. In contrast to the open conversion and morbidity outcomes, a learning curve pattern was confirmed in pathology endpoints. The learning curves in our settings validate the comparability of the results, despite the absence of National or Surgical Society driven training programs. However, the initiation of a formal LCRO training policy is necessary for the safe and efficient implementation of these procedures.



DOI: 10.4253/wjge.v14.i6.387

Figure 1 Cumulative sum analysis of operation duration in laparoscopic colorectal operations. CUSUM: Cumulative sum; LCRO: Laparoscopic colorectal operations.



DOI: 10.4253/wjge.v14.i6.387

Figure 2 Cumulative sum analysis of operation duration in laparoscopic colon operations. CUSUM: Cumulative sum; LCO: Laparoscopic colon operations.

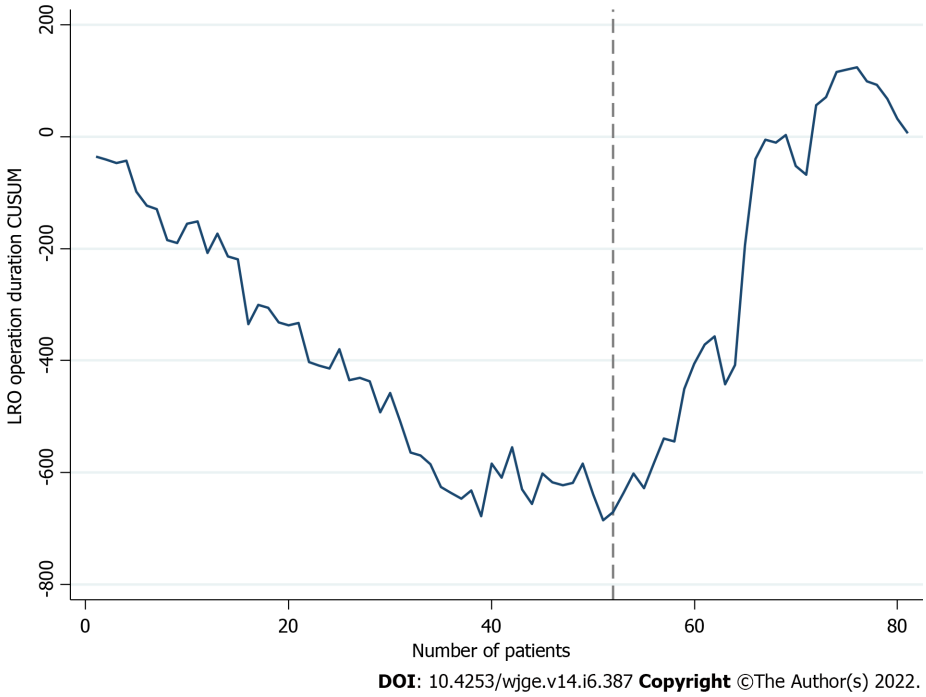


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Figure 3 Cumulative sum analysis of operation duration in laparoscopic rectal operations. CUSUM: Cumulative sum; LRO: Laparoscopic rectal operations.

ARTICLE HIGHLIGHTS

Research background

The introduction of structured training programs results in an enhanced learning process in laparoscopic colorectal surgery.

Research motivation

National training programs are not widely available, thus constraining the efficient adaptation of minimal invasive techniques in colorectal surgery.

Research objectives

To analyze the learning curve patterns in laparoscopic colorectal operations under a non-structured training setting.

Research methods

A retrospective analysis of a prospectively collected database was performed. Cumulative sum analysis and change point analysis were introduced for the evaluation of learning curve patterns.

Research results

In terms of operation duration, three learning curve phases were identified. A learning curve pattern was also confirmed in pathology endpoints, but not in the open conversion and complications outcomes.

Research conclusions

Laparoscopic colorectal operations under a non-structured training setting result in similar learning patterns with the respective structured training curves.

Research perspectives

The introduction of formal training programs in laparoscopic colorectal surgery is necessary for the safer and wider adoption of these techniques.

FOOTNOTES

Author contributions: Perivoliotis K, Baloyiannis I, and Tzovaras G designed the research study; Mamaloudis I, Volakakis G, and Valaroutsos A acquired the study data; Perivoliotis K and Baloyiannis I drafted the manuscript; Baloyiannis I and Tzovaras G critically revised and approved the final manuscript.

Institutional review board statement: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We consulted extensively with the IRB of University Hospital of Larissa who determined that our study did not need ethical approval since all procedures being performed were part of the routine care.

Informed consent statement: Informed consent was obtained from all individual participants included in the study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: The datasets generated during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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REFERENCES

1 **Yamanashi T**, Nakamura T, Sato T, Naito M, Miura H, Tsutsui A, Shimazu M, Watanabe M. Laparoscopic surgery for locally advanced T4 colon cancer: the long-term outcomes and prognostic factors. *Surg Today* 2018; **48**: 534-544 [PMID: 29288349 DOI: 10.1007/s00595-017-1621-8]
2 **Yamaguchi S**, Tashiro J, Araki R, Okuda J, Hanai T, Otsuka K, Saito S, Watanabe M, Sugihara K. Laparoscopic versus open resection for transverse and descending colon cancer: Short-term and long-term outcomes of a multicenter retrospective study of 1830 patients. *Asian J Endosc Surg* 2017; **10**: 268-275 [PMID: 28387060 DOI: 10.1111/ases.12373]
3 **Son GM**, Kim JG, Lee JC, Suh YJ, Cho HM, Lee YS, Lee IK, Chun CS. Multidimensional analysis of the learning curve for laparoscopic rectal cancer surgery. *J Laparoendosc Adv Surg Tech* 2010; **20**: 609-617 [DOI: 10.1089/Lap.2010.0007]
4 **Mackenzie H**, Miskovic D, Ni M, Parvaiz A, Acheson AG, Jenkins JT, Griffith J, Coleman MG, Hanna GB. Clinical and educational proficiency gain of supervised laparoscopic colorectal surgical trainees. *Surg Endosc* 2013; **27**: 2704-2711 [PMID: 23392980 DOI: 10.1007/s00464-013-2806-x]
5 **Rao PP**, Rao PP, Bhagwat S. Single-incision laparoscopic surgery - current status and controversies. *J Minim Access Surg* 2011; **7**: 6-16 [PMID: 21197236 DOI: 10.4103/0972-9941.72360]
6 **Kim CW**, Lee KY, Lee SC, Lee SH, Lee YS, Lim SW, Kim JG. Learning curve for single-port laparoscopic colon cancer resection: a multicenter observational study. *Surg Endosc* 2017; **31**: 1828-1835 [PMID: 27553791 DOI: 10.1007/s00464-016-5180-7]
7 **Georgiou PA**, Bhangu A, Brown G, Rasheed S, Nicholls RJ, Tekkis PP. Learning curve for the management of recurrent and locally advanced primary rectal cancer: a single team's experience. *Colorectal Dis* 2015; **17**: 57-65 [PMID: 25204543 DOI: 10.1111/codi.12772]
8 **Melich G**, Jeong DH, Hur H, Baik SH, Faria J, Kim NK, Min BS. Laparoscopic right hemicolectomy with complete mesocolic excision provides acceptable perioperative outcomes but is lengthy--analysis of learning curves for a novice minimally invasive surgeon. *Can J Surg* 2014; **57**: 331-336 [PMID: 25265107 DOI: 10.1503/cjs.002114]
9 **Tsai KY**, Kiu KT, Huang MT, Wu CH, Chang TC. The learning curve for laparoscopic colectomy in colorectal cancer at a new regional hospital. *Asian J Surg* 2016; **39**: 34-40 [PMID: 25959025 DOI: 10.1016/j.asjsur.2015.03.008]
10 **Rönnow C-F**, Uedo N, Toth E, Thorlacius H. Endoscopic submucosal dissection of 301 Large colorectal neoplasias: outcome and learning curve from a specialized center in Europe. *Endosc Int Open* 2018; **6**: E1340-8 [DOI:

10.1055/a-0733-3668]
11 **Lohsiriwat V**. Learning curve of enhanced recovery after surgery program in open colorectal surgery. *World J Gastrointest Surg* 2019; **11**: 169-178 [PMID: 31057701 DOI: 10.4240/wjgs.v11.i3.169]
12 **Symer MM**, Sedrakyan A, Yeo HL. Case Sequence Analysis of the Robotic Colorectal Resection Learning Curve. *Dis Colon Rectum* 2019; **62**: 1071-1078 [PMID: 31318771 DOI: 10.1097/DCR.0000000000001437]
13 **Gehrman J**, Angenete E, Björholt I, Lesén E, Haglind E. Cost-effectiveness analysis of laparoscopic and open surgery in routine Swedish care for colorectal cancer. *Surg Endosc* 2020; **34**: 4403-4412 [PMID: 31630289 DOI: 10.1007/s00464-019-07214-x]
14 **Prakash K**, Kamalesh NP, Pramil K, Vipin IS, Sylesh A, Jacob M. Does case selection and outcome following laparoscopic colorectal resection change after initial learning curve? *J Minim Access Surg* 2013; **9**: 99-103 [PMID: 24019686 DOI: 10.4103/0972-9941.115366]
15 **Naguib N**, Masoud AG. Laparoscopic colorectal surgery for diverticular disease is not suitable for the early part of the learning curve. A retrospective cohort study. *Int J Surg* 2013; **11**: 1092-1096 [DOI: 10.1016/j.ijsu.2013.09.013]
16 **Pendlimari R**, Holubar SD, Dozois EJ, Larson DW, Pemberton JH, Cima RR. Technical proficiency in hand-assisted laparoscopic colon and rectal surgery: determining how many cases are required to achieve mastery. *Arch Surg* 2012; **147**: 317-322 [PMID: 22184135 DOI: 10.1001/archsurg.2011.879]
17 **Tekkis PP**, Senagore AJ, Delaney CP, Fazio VW. Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections. *Ann Surg* 2005; **242**: 83-91 [PMID: 15973105 DOI: 10.1097/01.sla.0000167857.14690.68]
18 **Jenkins JT**, Currie A, Sala S, Kennedy RH. A multi-modal approach to training in laparoscopic colorectal surgery accelerates proficiency gain. *Surg Endosc* 2016; **30**: 3007-3013 [PMID: 26487223 DOI: 10.1007/s00464-015-4591-1]
19 **Rencuzogullari A**, Stocchi L, Costedio M, Gorgun E, Kessler H, Remzi FH. Characteristics of learning curve in minimally invasive ileal pouch-anal anastomosis in a single institution. *Surg Endosc* 2017; **31**: 1083-1092 [PMID: 27412123 DOI: 10.1007/s00464-016-5068-6]
20 **Hwang MR**, Seo GJ, Yoo SB, Park JW, Choi HS, Oh JH, Jeong SY. Learning curve of assistants in laparoscopic colorectal surgery: overcoming mirror imaging. *Surg Endosc* 2010; **24**: 2575-2580 [PMID: 20349091 DOI: 10.1007/s00464-010-1005-2]
21 **Ito M**, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y, Saito N. Influence of learning curve on short-term results after laparoscopic resection for rectal cancer. *Surg Endosc* 2009; **23**: 403-408 [PMID: 18401643 DOI: 10.1007/s00464-008-9912-1]
22 **Dinçler S**, Koller MT, Steurer J, Bachmann LM, Christen D, Buchmann P. Multidimensional analysis of learning curves in laparoscopic sigmoid resection: eight-year results. *Dis Colon Rectum* 2003; **46**: 1371-8; discussion 1378 [PMID: 14530677 DOI: 10.1007/s10350-004-6752-5]
23 **Miskovic D**, Ni M, Wyles SM, Tekkis P, Hanna GB. Learning curve and case selection in laparoscopic colorectal surgery: systematic review and international multicenter analysis of 4852 cases. *Dis Colon Rectum* 2012; **55**: 1300-1310 [PMID: 23135590 DOI: 10.1097/DCR.0b013e31826ab4dd]
24 **Chen G**, Liu Z, Han P, Li JW, Cui BB. The learning curve for the laparoscopic approach for colorectal cancer: a single institution's experience. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 17-21 [PMID: 23317439 DOI: 10.1089/lap.2011.0540]
25 **Haas EM**, Nieto J, Ragupathi M, Aminian A, Patel CB. Critical appraisal of learning curve for single incision laparoscopic right colectomy. *Surg Endosc* 2013; **27**: 4499-4503 [PMID: 23877765 DOI: 10.1007/s00464-013-3096-z]
26 **Miskovic D**, Wyles SM, Carter F, Coleman MG, Hanna GB. Development, validation and implementation of a monitoring tool for training in laparoscopic colorectal surgery in the English National Training Program. *Surg Endosc* 2011; **25**: 1136-1142 [PMID: 20835723 DOI: 10.1007/s00464-010-1329-y]
27 **Toledano Trincado M**, Sánchez Gonzalez J, Blanco Antona F, Martín Esteban ML, Colao García L, Cuevas Gonzalez J, Mayo Iscar A, Blanco Alvarez JI, Martín del Olmo JC. How to reduce the laparoscopic colorectal learning curve. *JSLS* 2014; **18** [PMID: 25392640 DOI: 10.4293/JSLS.2014.00321]
28 **Ni M**, Mackenzie H, Widdison A, Jenkins JT, Mansfield S, Dixon T, Slade D, Coleman MG, Hanna GB. What errors make a laparoscopic cancer surgery unsafe? *Surg Endosc* 2016; **30**: 1020-1027 [PMID: 26099620 DOI: 10.1007/s00464-015-4289-4]
29 **Kye BH**, Kim JG, Cho HM, Kim HJ, Suh YJ, Chun CS. Learning curves in laparoscopic right-sided colon cancer surgery: a comparison of first-generation colorectal surgeon to advance laparoscopically trained surgeon. *J Laparoendosc Adv Surg Tech A* 2011; **21**: 789-796 [PMID: 21854205 DOI: 10.1089/lap.2011.0086]
30 **Leong S**, Cahill RA, Mehigan BJ, Stephens RB. Considerations on the learning curve for laparoscopic colorectal surgery: a view from the bottom. *Int J Colorectal Dis* 2007; **22**: 1109-1115 [PMID: 17404746 DOI: 10.1007/s00384-007-0302-2]
31 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; **4**: e296 [PMID: 17941714 DOI: 10.1371/journal.pmed.0040296]
32 **Choi DH**, Jeong WK, Lim SW, Chung TS, Park JI, Lim SB, Choi HS, Nam BH, Chang HJ, Jeong SY. Learning curves for laparoscopic sigmoidectomy used to manage curable sigmoid colon cancer: single-institute, three-surgeon experience. *Surg Endosc* 2009; **23**: 622-628 [PMID: 18270771 DOI: 10.1007/s00464-008-9753-y]
33 **Li JC**, Hon SS, Ng SS, Lee JF, Yiu RY, Leung KL. The learning curve for laparoscopic colectomy: experience of a surgical fellow in an university colorectal unit. *Surg Endosc* 2009; **23**: 1603-1608 [PMID: 19452217 DOI: 10.1007/s00464-009-0497-0]
34 **Stam M**, Draaisma WA, Pasker P, Consten E, Broeders I. Sigmoid resection for diverticulitis is more difficult than for malignancies. *Int J Colorectal Dis* 2017; **32**: 891-896 [PMID: 28084549 DOI: 10.1007/s00384-017-2756-1]
35 **Shanker BA**, Soliman M, Williamson P, Ferrara A. Laparoscopic Colorectal Training Gap in Colorectal and Surgical Residents. *JSLS* 2016; **20** [PMID: 27493468 DOI: 10.4293/JSLS.2016.00024]
36 **Li JCM**, Lo AWI, Hon SSF, Ng SSM, Lee JFY, Leung KL. Institution learning curve of laparoscopic colectomy-a multi-dimensional analysis. *Int J Colorectal Dis* 2012; **27**: 527-533 [DOI: 10.1007/s00384-011-1358-6]

37 **Park IJ**, Choi GS, Lim KH, Kang BM, Jun SH. Multidimensional analysis of the learning curve for laparoscopic colorectal surgery: lessons from 1,000 cases of laparoscopic colorectal surgery. *Surg Endosc* 2009; **23**: 839-846 [PMID: 19116741 DOI: 10.1007/s00464-008-0259-4]

38 **Zhang XM**, Wang Z, Liang JW, Zhou ZX. Seniors have a better learning curve for laparoscopic colorectal cancer resection. *Asian Pac J Cancer Prev* 2014; **15**: 5395-5399 [PMID: 25041008 DOI: 10.7314/apjcp.2014.15.13.5395]

39 **Bennett CL**, Stryker SJ, Ferreira MR, Adams J, Beart RW Jr. The learning curve for laparoscopic colorectal surgery. Preliminary results from a prospective analysis of 1194 laparoscopic-assisted colectomies. *Arch Surg* 1997; **132**: 41-4; discussion 45 [PMID: 9006551 DOI: 10.1001/archsurg.1997.01430250043009]

40 **Kiran RP**, El-Gazzaz GH, Vogel JD, Remzi FH. Laparoscopic approach significantly reduces surgical site infections after colorectal surgery: data from national surgical quality improvement program. *J Am Coll Surg* 2010; **211**: 232-238 [PMID: 20670861 DOI: 10.1016/j.jamcollsurg.2010.03.028]

41 **Li Destri G**, Di Carlo I, Scilletta R, Scilletta B, Puleo S. Colorectal cancer and lymph nodes: the obsession with the number 12. *World J Gastroenterol* 2014; **20**: 1951-1960 [PMID: 24587671 DOI: 10.3748/wjg.v20.i8.1951]

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ORIGINAL ARTICLE

Observational Study

Role of endoscopic ultrasound and cyst fluid tumor markers in diagnosis of pancreatic cystic lesions

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Abstract

BACKGROUND

Pancreatic cystic lesions (PCLs) are common in clinical practice. The accurate classification and diagnosis of these lesions are crucial to avoid unnecessary treatment of benign lesions and missed opportunities for early treatment of potentially malignant lesions.

AIM

To evaluate the role of cyst fluid analysis of different tumor markers such as cancer antigens [*e.g.*, cancer antigen (CA)19-9, CA72-4], carcinoembryonic antigen (CEA), serine protease inhibitor Kazal-type 1 (SPINK1), interleukin 1 beta (IL1-β), vascular endothelial growth factor A (VEGF-A), and prostaglandin E2 (PGE2)], amylase, and mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

METHODS

This study included 76 patients diagnosed with PCLs using different imaging modalities. All patients underwent endoscopic ultrasound (EUS) and EUS-fine needle aspiration (EUS-FNA) for characterization and sampling of different PCLs.

RESULTS

The mean age of studied patients was 47.4 ± 11.4 years, with a slight female predominance (59.2%). Mucin stain showed high statistical significance in predicting malignancy with a sensitivity of 87.1% and specificity of 95.56%. It also showed a positive predictive value and negative predictive value of 93.1% and 91.49%, respectively ($P < 0.001$). We found that positive mucin stain, cyst fluid glucose, SPINK1, amylase, and CEA levels had high statistical significance ($P < 0.0001$). In contrast, IL-1β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance. Univariate regression analysis for prediction of malignancy in PCLs showed a statistically significant positive correlation with mural nodules, lymph nodes, cyst diameter, mucin stain, and cyst fluid CEA. Meanwhile, logistic multivariable regression analysis proved that mural nodules, mucin stain, and SPINK1 were independent predictors of malignancy in cystic pancreatic lesions.

CONCLUSION

EUS examination of cyst morphology with cytopathological analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 could be used as promising markers to predict malignant pancreatic cysts.

Key Words: Pancreatic cystic neoplasm; Mucinous cystic neoplasm; Intraductal papillary mucinous neoplasm; Mucin stain; Amylase

Core Tip: Nowadays, the awareness of pancreatic cystic lesions has become an essential issue, especially with the increased incidence of asymptomatic pancreatic cysts in the general population. Therefore, the proper diagnosis, meticulous differentiation, and staging of these pancreatic cystic lesions are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions. Endoscopic ultrasound examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the diagnostic capability. Also, many developed markers are valuable for predicting a malignant pancreatic cyst.

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INTRODUCTION

Pancreatic cystic lesions (PCLs) are not rare; they vary from a simple benign cyst to a highly malignant one[1]. Awareness of these lesions has increased in recent years, especially with the increased incidence of asymptomatic pancreatic cysts in the general population primarily due to improved detection by different advanced imaging modalities[2,3]. Therefore, the proper diagnosis, meticulous differentiation, and staging of these PCLs are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions[4,5].

Endoscopic ultrasound (EUS) has become an indispensable tool for diagnosing many pancreatic lesions; it has a benefit for better evaluation of number, location, dimensions, wall thickness, and the content of pancreatic cysts. Also, it is crucial in distinguishing the internal septae and solid areas within the cysts[6].

The morphological features of PCLs are not independent factors in differentiating malignant from nonmalignant lesions. The combination of both EUS-fine needle aspiration (EUS-FNA) findings with cystic fluid tumor marker analysis, along with clinical, radiologic, histologic, genetic, and molecular characteristics, enhances the diagnostic accuracy for PCLs and helps to construct a novel model in the era of PCL diagnosis[4].

Currently, many tumor markers, both in the serum and in pancreatic cyst fluid (CF), have been widely studied as a tool for distinguishing mucinous/malignant and non-mucinous pancreatic cystic lesions, such as carcinoembryonic antigen (CEA), cancer antigen (CA)19-9, CA125, CA15-3, and CA72-4 [7].

MATERIALS AND METHODS

Study design and aims

In this single tertiary referral center prospective study, the samples were collected and stored, and then all markers were detected in the same specimens in the same time. The study aimed primarily to evaluate the role of cyst fluid amylase and tumor markers such as CA 19-9, CEA, serine protease inhibitor Kazal-type 1 (SPINK1), IL1-β, CA 72-4, vascular endothelial growth factor A (VEGF-A), and prostaglandin E2 (PGE2) in addition to mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

Patients and recruitment

This prospective study was conducted on 76 patients diagnosed with PCLs using different imaging modalities such as computed tomography (CT), EUS, abdominal ultrasound, or magnetic resonance imaging (MRI). The candidates were recruited over 3 years from the Gastroenterology, Endoscopy, and Hepatology Unit, Internal Medicine Department, Kasr Al-Ainy, Cairo University. Fluid analysis was performed for CA 19-9, CA 72-4, CEA, VEGF-1, SPINK-1, IL1-b, PGE2, amylase, mucin stain, and cytopathology. We compared these data with the final diagnosis based on histopathology after surgical resection, positive cytopathology (positive for malignancy), and a long period of follow-up of the patients for at least 18 mo.

All patients underwent EUS examination for cyst characterization and sampling of the cystic lesions. All included patients were above 18 years of age. Patients included in this study were diagnosed with

large pancreatic cysts (larger than 3 cm), suspicious intraductal papillary mucinous neoplasm (IPMN), or pancreatic duct dilatation proved by magnetic resonance cholangiopancreatography. However, patients with small cysts (less than 1 cm), calculous cholecystitis, a potential risk for anesthesia, or a bleeding tendency (international normalized ratio > 1.5, or severe thrombocytopenia, with platelet count < 50000/mm^3) and patients who refused to participate were excluded from the study. Also, those who missed the follow-up were ruled out from the study. Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki.

Examination procedure

All the patients, after thorough full history taking and clinical examination, were subjected to: (1) EUS examination using a linear Echoendoscope PENTAX EG3870UTK (HOYA Corporation, PENTAX Life Care Division, Showanomori Technology Center, Tokyo, Japan) connected to an ultrasound unit Hitachi AVIUS machine (Hitachi Medical Systems, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. For EUS-FNA, we used the Cook 19G and 22G needles (Echotip; Wilson-Cook, Winston Salem, NC). Prophylactic ceftriaxone (1 gm) was administered before the procedure; (2) characterization of the PCLs. All the characteristics of the PCLs were documented, including localization, number, dimensions, wall thickness, presence of septations or mural nodules, calcification, lymph nodes, and cystic dilatation of the main pancreatic duct. The color, transparency, and viscosity of the CF were also recorded; and (3) evacuation of the cystic fluid entirely with a single needle pass. Aspirated material inside the needle was spread over dry slides. Also, a proportion of the fluid sample (at least 2 mL) was sent for cytopathological examination, including mucin staining using alcian blue stain. At least 5 mL of cyst fluid was analyzed for CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, PGE2, and CA-19-9 using two-site immunoassays (Beckman Coulter). Amylase was measured by the enzymatic colorimetric assay on a modular system (Roche).

Cysts were considered malignant when any of the following is present: (1) Cytopathological detection of malignancy; (2) presence of metastasis in the absence of other concomitant malignancies; (3) presence of mural nodules that progress in size within 6 mo; and (4) postoperative pathological diagnosis of malignancy if available. Cysts were considered benign when proved negative for malignancy by cytopathological examination and follow-up for 18 mo without increasing its size, the appearance of mural nodules or metastasis, or occurrence of obstructive jaundice.

The overall complication rate of EUS-FNA in the prospective series ranges from 0% to 2.5%[8]. Such complications include pain, infection, bleeding, acute pancreatitis, perforation of the esophagus or duodenum, bile peritonitis, and seeding of tumorous cells along the needle track[9]. Therefore, a prophylactic antibiotic in the form of 1 gm IM or slow IV third-generation cephalosporin was administered 6 h before the procedure. No major complications occurred in our series. However, self-limiting intracystic bleeding occurred in one patient, and mild pain occurred in three patients. All patients were discharged on the same day, and no hospital admission was needed.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences v. 25. Numerical data are summarized using the mean and standard deviation, median, or range, as appropriate. Categorical data are summarized as numbers and percentages. Estimates of the frequency were calculated using the numbers and percentages. Numerical data were explored for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. To measure the association between variables: (1) Chi-square or Fisher's tests were used to compare independent groups concerning categorical data; (2) kappa statistics were computed to test the agreement between categorical variables. Their values ranged from zero to one; (3) the Mann-Whitney *U* test implemented comparisons between two groups for non-normally distributed numeric variables; and (4) *P* value ≤ 0.05 was considered significant.

RESULTS

This study included 76 patients [31 males (40.8%) and 45 females (59.2%)] with a mean age of 47.4 ± 11.4 years (Table 1).

EUS evaluation showed that most patients had a unilocular cyst (40 patients, 52.6%), while 36 patients (47.4%) had a multilocular cyst. Mural nodules were found in 24 patients (31.6%). In addition, most cysts had thin walls (77.6%) and clear contents (78.9%). Calcifications and lymph nodes were not found in 92.1% and 82.9% of patients, respectively. The pancreatic duct was dilated in 10 patients (13.2%) (Table 2).

Pancreatic cysts were diagnosed as being malignant/potentially malignant or benign in 38.2% and 61.8% of patients, respectively. Malignant cysts included mucinous cystadenocarcinoma (14.5%) (Figure 1A) and pancreatic adenocarcinoma (5.3%). On the other hand, potentially malignant cysts included IPMN with low (7.9%) and high-grade dysplasia (13.2%) and mucinous cystadenoma. Benign cysts included serous and mucinous cystic neoplasms (17.1%), pseudocysts (39.5%) (Figure 1B), and

Table 1 Descriptive data of included patients

Gender	Number	Percent (%)
Male	31	40.80%
Female	45	59.20%
Total	76	100%

Table 2 Endoscopic ultrasound findings of studied patients

EUS finding		Number	Percent (%)
Loculation	Unilocular	40	0.526
	Multilocular	36	0.474
Mural nodules	No	52	0.684
	Yes	24	0.316
Wall	Thin Wall	59	0.776
	Thick Wall	17	0.224
Content	Clear	60	0.789
	Turbid	16	0.211
Calcification	No	70	0.921
	Yes	6	0.079
LNs	No	63	0.829
	Yes	13	0.171
Pancreatic duct dilation	No	66	0.868
	Yes	10	0.132

EUS: Endoscopic ultrasound.

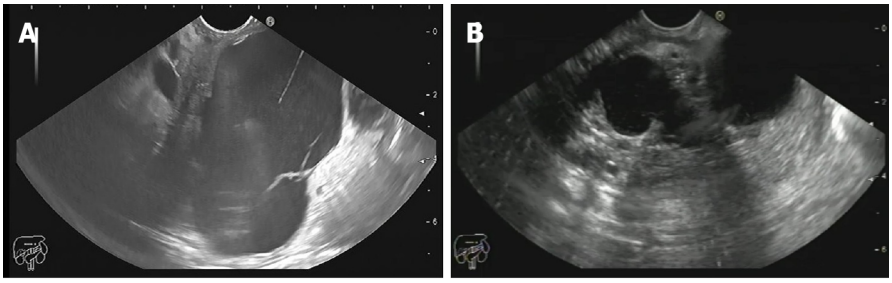

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Figure 1 Pancreatic body mucinous cystadenoma. A: Pancreatic body mucinous cystadenoma; B: Bilocular inflammatory pseudocyst in the gastric body.

cystic lymphangioma (1.3%) (Table 3).

Evaluating PCLs using mucin stain to differentiate between mucinous and non-mucinous pancreatic cystic lesions showed a sensitivity of 100%, specificity of 94%, and accuracy of 96.04% (Table 4). Also, we found that there was high statistical significance for mucin stain in predicting malignancies with a sensitivity of 87.1%, specificity of 95.56%, positive predictive value (PPV) of 93.1%, and negative predictive value (NPV) of 91.49% (P value < 0.001) (Table 5).

The median CF CEA level was 90 (8.39- 2750) ng/mL. Also, the median CF SPINK1 level was 0.56 (0.35-0.97) ng/mL, and the median CF glucose level was 50 mg/dL (Table 6). When we categorized the CF level of CEA above and below 192 ng/mL, the malignant/potentially malignant cysts were more likely to have a CEA level above 192 ng/mL (P = 0.001), as shown in Table 7.

As shown in Table 6, CF CEA level and CF amylase were significantly higher in malignant/potentially malignant cysts than in benign cysts with a median of 15.8 *vs* 6.4 and 130.5 *vs* 3060 (P = 0.004

Table 3 Final diagnosis

Final diagnosis	Number	Percent (%)
Pancreatic pseudocyst	30	39.5
Pancreatic pseudocyst with WOPN	1	1.3
Serous cystadenoma	13	17.1
Mucinous cystadenoma	11	14.5
IPMN (high grade dysplasia)	10	13.2
IPMN (low grade dysplasia)	6	7.9
Pancreatic adenocarcinoma	4	5.3
Cystic lymphangioma	1	1.3
Total	76	100

IPMN: Intraductal papillary mucinous neoplasm; WOPN: Walled-off pancreatic necrosis.

Table 4 Mucin stain in detecting mucinous from non-mucinous pancreatic cystic lesions

Statistic	Value	95%CI
Sensitivity	100%	86.77% to 100%
Specificity	94%	83.45% to 98.75%
Positive likelihood ratio	16.67	5.56 to 49.93
Negative likelihood ratio	0	
Disease prevalence	34.21%	23.71% to 45.99%
Positive predictive value	89.66%	74.31% to 96.29%
Negative predictive value	100%	
Accuracy	96.05%	88.89% to 99.18%

Table 5 Mucin stain in detecting benign from malignant pancreatic cystic lesions

Statistic	Value	95%CI
Sensitivity	87.10%	70.17% to 96.37%
Specificity	95.56%	84.85% to 99.46%
Positive likelihood ratio	19.60	5.02 to 76.47
Negative likelihood ratio	0.14	0.05 to 0.34
Disease prevalence	40.79%	29.65% to 52.67%
Positive predictive value	93.10%	77.58% to 98.14%
Negative predictive value	91.49%	81.12% to 96.41%
Accuracy	92.11%	83.60% to 97.05%

and 0.034, respectively). Also, CF amylase and CF CEA showed statistical significance in predicting malignancy (P = 0.028 and < 0.001, respectively). Furthermore, the SPINK1 level in CF was significantly higher in malignant/potentially malignant cysts compared to benign ones (0.91 *vs* 0.47, P = 0.001). Meanwhile, glucose was markedly consumed in malignant/potentially malignant cysts than in benign cysts (21.5 *vs* 68.5, P = 0.0001) (Table 7).

Comparing different CF markers in predicting malignant PCLs among the studied patients revealed that positive Mucin stain, CF glucose, SPINK1, amylase, and CEA showed high statistical significance (P < 0.0001, 0.0001, 0.001, 0.034, and 0.004, respectively). However, IL1-β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance (Table 8).

Table 6 Cyst fluid carcinoembryonic antigen, serine protease inhibitor Kazal-type 1, and glucose level in studied patients

Biochemical test	Median (IQR)	Range
CEA (ng/ml)	90 (8.78- 1560)	(5-100000)
SPINK1 (ng/ml)	0.56 (0.35-0.97)	(0.1-2.32)
Glucose (mg/dl)	50 (10-84)	(2-171)

IQR: Interquartile range.

Table 7 Cystic fluid analysis of malignant/potentially and benign cysts

Variable	Benign group(n = 45)	Malignant group(n = 31)	P value
Mucin stain positivity	2 (4.4%)	27 (87.1%)	< 0.0001
Number (%)			
Glucose (mg/dl)	21.5 (4-45)	68.5 (47-87)	0.0001
median (IQR)			
IL1b (pg/mL)	0.37 (0.58)	0.34 (0.45)	0.845
(median, IQR)			
CA 72-4 (U/mL)	6.36 (9.7)	7.4 (7.6)	0.323
(median, IQR)			
VEGF-A (pg/ml)	707.8 (1056)	736.9 (2262)	0.866
(median, IQR)			
VEGFR2 (pg/ml)	2.5 (5.3)	1.3 (3)	0.281
(median, IQR)			
SPINK1 (ng/ml)	0.91 (0.41-1.45)	0.47 (0.3-0.72)	0.001
median (IQR)			
PGE2 (pg/ml)	307.2 (131)	409.7 (176)	0.121
(median, IQR)			
CF amylase (U/L)	130.5 (353)	3060 (5191)	0.034
(median, IQR)			
CF CEA (ng/ml)	6.4 (234)	15.8 (2532)	0.004
(median, IQR)			
CEA (> 192 ng/mL)	15	5	0.001

CEA: Carcinoembryonic antigen; CF: Cyst fluid; IQR: Interquartile range; VEGFR2: Vascular endothelial growth factor receptor 2; SPINK1: Serine protease inhibitor Kazal-type 1.

Univariate regression analysis showed a statistically significant association between malignancy in PCLs and mural nodules, lymph nodes, cyst diameter, mucin stain, CF CEA, SPINK1, and CEA level > 192 ng/mL. In comparison, multivariable regression analysis proved that mural nodules, mucin stain, SPINK1, and CEA level > 192 ng/mL were independent predictors of malignancy in cystic pancreatic lesions (Table 9).

Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy of CF CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, PGE2, and CA-19-9 in predicting malignant cysts. It revealed that the area under the curve was comparable for CEA, glucose, and SPINK1 (0.75, 0.76, and 0.72, respectively) (Figures 2A-C).

The sensitivity of EUS diagnosis in detecting malignant and premalignant pancreatic cysts was 66.7%, while 69.2% for the specificity, 60% PPV, and 75% NPV with an overall accuracy of 68.2% (Table 10).

Out of 76 patients, two patients died. Both patients had pancreatic adenocarcinoma. Most of the patients showed a stationary course (40 patients, 52.6%), and only three patients (3.9%) ran a regressive

Table 8 Value of different variables in predicting malignancy

Variable	Criterion	Specificity	Sensitivity	PPV	NPV	*P* value	AUC
Age	> 35	0.244	1	0.4745	1	0.605	0.534
Mucin stain		0.9556	0.871	0.931	0.9149	< 0.001	0.913
Glucose (mg/dL)	≤ 42	0.7353	0.8478				0.76
IL1b (pg/mL)	< 1.13	0.209	0.9	0.4363	0.7464	0.761	0.521
CA 72-4 (U/mL)	> 4.3138	0.467	0.677	0.4657	0.678	0.32	0.567
VEGF-A (pg/mL)	> 1221.7	0.844	0.29	0.561	0.634	0.87	0.511
VEGFR2 (pg/ml)	> 6.601	0.933	0.29	0.7482	0.657	0.301	0.573
SPINK1 (μg/L)	≥ 0.58	0.6533	0.7059	0.708	0.623		0.72
PGE2 (pg/ml)	> 311.77	0.556	0.8	0.5529	0.802	0.102	0.683
CF amylase (U/L)	> 270	0.71	0.711	0.629	0.781	0.028	0.644
CF CEA (ng/ml)	> 8	0.742	0.689	0.622	0.795	< 0.001	0.761

CA: Cancer antigen; CF: Cyst fluid; VEGFR2: Vascular endothelial growth factor receptor 2; PPV: Positive predictive value; NPV: Negative predictive value.

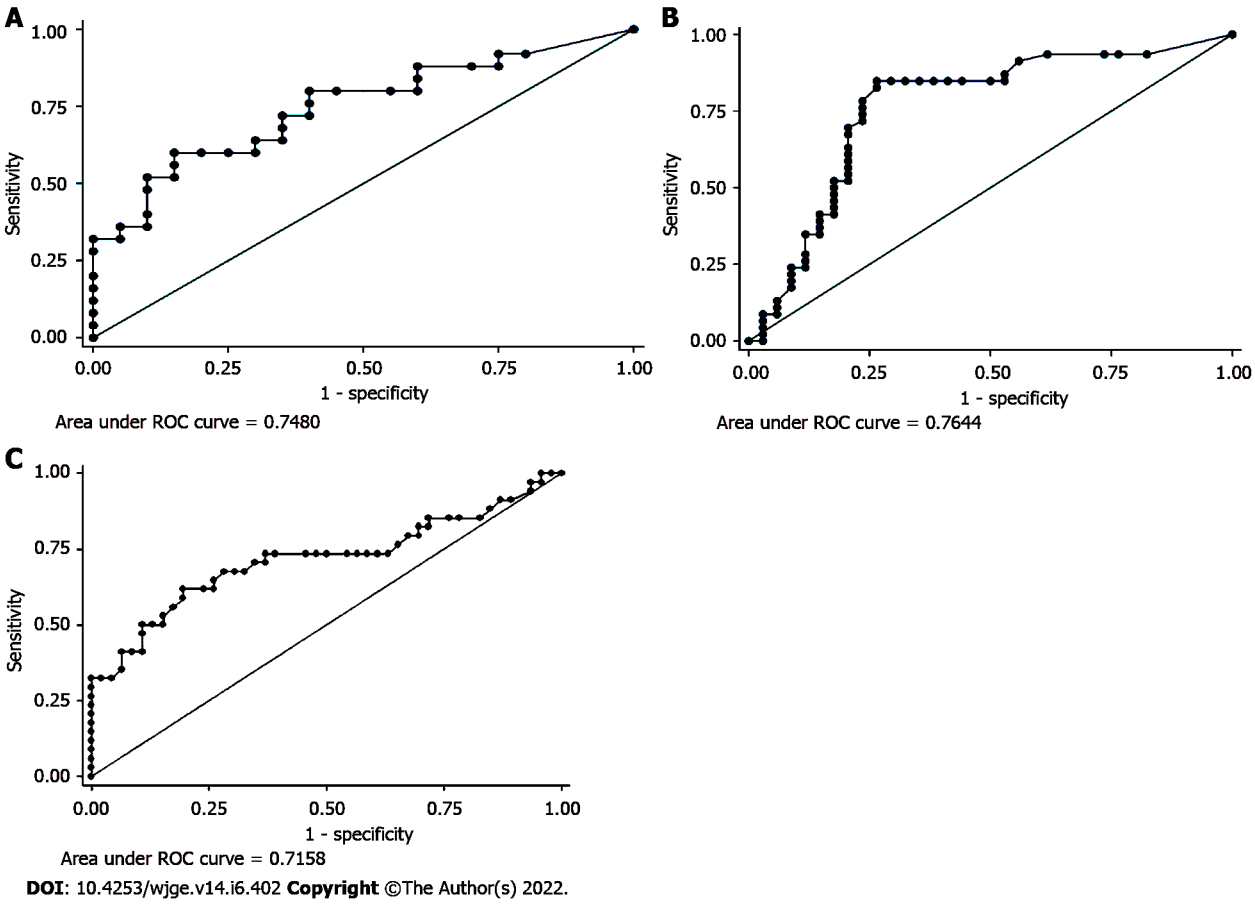

Figure 2 Receiver operating characteristic curve analysis. A: Cyst fluid carcinoembryonic antigen level; B: Glucose level in cyst fluid; C: Cyst fluid serine protease inhibitor Kazal-type 1 level. ROC: Receiver operating characteristic.

course, as demonstrated in Table 11. Two patients with inflammatory pseudocyst underwent a percutaneous pig-tail insertion; one of them was complicated by abscess formation and proceeded to surgery. Most of the patients required no intervention (56 patients, 73.7%). However, some patients were referred to surgeries (17 patients, 22.4%), and only one patient underwent cystogastrostomy, as demonstrated in Table 12.

Table 9 Logistic regression analysis for predictors of malignancy in cystic pancreatic lesions

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age	1.06 (0.97-1.06)	0.4312		
Mural nodules	6.6 (2.3- 19.3)	0.0006	5.7 (1.37-24.6)	0.0172
Wall thickness	1.39 (0.47-4.124)	0.5514		
LNs	11.82 (2.4-58.4)	0.0024	0.14 (0.006-3.3)	0.2219
Content	0.59 (0.18-1.923)	0.3851		
Loculation	1.1 (0.43-2.68)	0.8826		
Calcification	1.5 (0.28-7.97)	0.6342		
Shortest Diameter	0.965 (0.94-0.99)	0.0189	1.06 (0.92-1.22)	0.4044
Longest Diameter	0.971(0.95-0.99)	0.0112	0.913 (0.81- 1.03)	0.1326
Mucin Stain	145 (24.8-847.2)	< 0.0001	82.4 (12.1-561)	< 0.0001
Glucose	0.97 (0.96-0.99)	> 0.001	0.99 (0.97-1.01)	0.48
IL1b (pg/mL)	0.91 (0.702-1.18)	0.496		
CA 72-4	1.02 (0.98-1.053)	0.3017		
VEGF-A	1.0001(0.99-1.0005)	0.5782		
VEGFR2	1.14 (0.99-1.318)	0.0782		
SPINK1	9.09 (2.62-31.59)	0.001	23.65 (3.10-180.62)	0.002
PGE2 (pg/mL)	1.01 (0.999-1.02)	0.0798		
CF Amylase	1 (1-1)	0.8593		
CF CEA	1.0003 (1.0001-1.0005)	0.0152	1.0001 (0.99-1.0006)	0.5978
CEA > 192 (ng/mL)	6.47 (2.05-20.42)	0.001	14.12 (2.39-83.22)	0.003

OR: Odds ratio; CI: Confidence interval; LNs: Lymph-nodes; CF: Cyst fluid; CA: Cancer antigen; CEA: Carcinoembryonic antigen; SPINK1: Serine protease inhibitor Kazal-type 1; IL1-β: Interleukin 1 beta; CA 72-4: Human cancer antigen 72-4; VEGF-A: Vascular endothelial growth factor A; VEGFR2: Vascular endothelial growth factor receptor 2, PGE2: Prostaglandin E2.

Table 10 Performance of EUS diagnosis for malignant/premalignant and benign cysts

Statistic	Value	95%CI
Sensitivity	0.6667	40.99% to 86.66%
Specificity	0.6923	48.21% to 85.67%
Positive predictive value	0.6	43.60% to 74.42%
Negative predictive value	0.75	59.79% to 85.82%
Accuracy	0.6818	52.42% to 81.39%

DISCUSSION

There are great challenges in diagnosing and managing PCLs that have become a common problem faced by many physicians and surgeons[10]. Some PCLs have a malignant potential with a significant risk of developing invasive cancer[11]. Therefore, the accurate classification and diagnosis of pancreatic cysts provide a potential for preventing and early detection of pancreatic cancer. On the other hand, misdiagnosis or unnecessary surgeries may lead to high cost and harm to the patients[10].

Unfortunately, imaging modalities such as CT and MRI have insufficient sensitivity and specificity to characterize PCLs and provide a suboptimal classification and diagnosis due to poor interobserver variability[12].

Table 11 Follow-up data of studied patients

Follow-up	Stationary	Regressive	No-recurrence	Progressive	Died
Pancreatic pseudocyst (n = 30)	27 (35.5%)	3 (3.9%)	0	0	0
Pancreatic pseudocyst with WOPN (n = 1)	0	0	1 (1.3%)	0	0
Serous cystadenoma (n = 13)	12 (15.7%)	0	1 (1.3%)	0	0
Mucinous cystadenoma (n = 10)	9	0	1 (1.3%)	0	0
Mucinous cystadenocarcinoma (n = 1)	0	0	0	1	0
IPMN (high grade dysplasia) (n = 10)	3	0	7	0	0
IPMN (low grade dysplasia) (n = 6)	6	0	0	0	0
Pancreatic adenocarcinoma (n = 4)	0	0	2 (2.6%)	0	2 (2.6%)
Cystic lymphangioma (n = 1)	1 (1.3%)	0	0	0	0
Total (n = 76)	40 (52.6%)	3 (3.9%)	5 (6.5%)	0	2 (2.6%)

Table 12 Intervention required for studied patients

Intervention required	No	Surgery	Pig-tail drainage	Cysto-gastrostomy
Pancreatic pseudocyst (n = 30)	26 (34.2%)	1 (1.3%)	2 (2.6%)	1 (1.3%)
Pancreatic pseudocyst with WOPN (n = 1)	0	1 (1.3%)	0	0
Serous cystadenoma (n = 13)	12 (15.8%)	1 (1.3%)	0	0
Mucinous cystadenoma (n = 10)	9 (11.7%)	1 (1.3%)	0	0
Mucinous cystadenocarcinoma (n = 1)	1 (1.3%)	0	0	0
IPMN (high grade dysplasia) (n = 10)	1 (1.3%)	9 (11.8%)	0	0
IPMN (low grade dysplasia) (n = 6)	6 (7.9%)	0	0	0
Pancreatic adenocarcinoma (n = 4)	0	4 (5.2%)	0	0
Cystic lymphangioma (n = 1)	1 (1.3%)	0	0	0
Total (n = 76)	56 (73.7%)	17 (22.4%)	2 (2.6%)	1 (1.3%)

EUS is considered the most sensitive tool in delineating the pancreatic cyst characteristics with the capacity to identify the presence of mural nodules and solid components[13]. Also, it has a benefit in enabling EUS-FNA for cytology[14]. Nonetheless, cytology still has a limited diagnostic yield with a pooled sensitivity of 63% and specificity of 88%[15].

Owing to the limited diagnostic accuracy for different pancreatic cysts with the current diagnostic modalities, analysis of the pancreatic CF obtained *via* EUS-FNA could improve the diagnostic accuracy for pancreatic cysts and help determine the malignant potentiality. Therefore, there is still a growing research interest in discovering and validating novel CF biomarkers that may improve diagnostic accuracy. The present study was designed to determine the role of CF amylase and tumor markers such as CA 19-9, CEA, SPINK1, IL1-β, CA 72-4, VEGF-A, and PGE2 in addition to mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

The presence of solid components inside the cyst on imaging could be a significant predictor of malignancy, as reported in many studies[16-18]. Also, we found that the presence of mural nodules was highly predictive of malignancy in univariate and multivariate logistic regression analysis (P = 0.0006 and 0.0172, respectively) along with cyst diameter (P = 0.0189 for shortest diameter and 0.0112 for longest diameter) and lymph node enlargement (P = 0.0024).

In a study conducted by Okasha *et al*[19] analyzing the CF amylase of 44 patients, they concluded that pancreatic CF amylase level could differentiate between malignant/potentially malignant and benign cysts with a sensitivity of 58%, specificity of 75%, PPV of 73%, NPV of 60%, and accuracy of 66%.

In our study, CF CEA level and CF amylase were significantly higher in malignant/potentially malignant cysts than in benign cysts (P = 0.004 and 0.034, respectively). This finding agrees with other studies stating that pancreatic CF CEA offers the best diagnostic performance than any other single test, especially in differentiating mucinous and non-mucinous cysts[20].

A large multi-institutional study conducted on 1861 patients reported that CEA > 192 ng/mL could differentiate mucinous from non-mucinous cysts with an accuracy of 77%[21]. Their findings are in

concordance with our study that reported that the malignant/potentially malignant cysts had CEA levels above 192 ng/mL ($P = 0.001$).

In CF, positive mucin stain was significantly more frequent in malignant cysts (87.1%) ($P < 0.0001$). Twenty-seven cysts were positive for mucin stain, with a sensitivity of 87.1% and specificity of 95.56% in differentiating benign from malignant PCLS. Also, mucin staining differentiates mucinous from non-mucinous cysts with a sensitivity and specificity of 100% and 94%, respectively. The results in the current study were more compatible with an Egyptian study by Okasha and his colleagues. They showed that pancreatic CF positive mucin stain was 85% sensitive and 95% specific in detecting mucinous or non-mucinous pancreatic cysts with a 92% PPV, 91% NPV, and 91% accuracy. Also, positive mucin staining was 63% sensitive and 97% specific in differentiating malignant/potentially malignant from benign pancreatic cysts with a PPV of 96%, NPV of 72%, and overall accuracy of 80%. This outcome is in concordance with a recent study by Okasha and his colleagues that showed that a CF positive mucin stain has a sensitivity of 85.5% and specificity of 86.1% for detecting mucinous cystic neoplasm with a 72.3% PPV, 93.3% NPV, and 85.9% accuracy[4]. Many studies also reported that the mucin staining could be complementary to cyst CEA levels and cytology, and when one out of three was found to be positive, this increases the sensitivity to 92% and specificity to 52%, as in a study conducted by Morris-Stiff *et al*[22].

In our study, CF glucose was markedly consumed in malignant/potentially malignant cysts than in benign cysts (21.5 *vs* 68.5, $P = 0.0001$). Since glucose is a simple and cheap biomarker, it could be used as a marker for differentiation between benign and malignant pancreatic cysts with a relatively low cost [23-25].

In 2004, Raty *et al*[26] were the first to evaluate the role of CF SPINK1 in differentiating potentially malignant from benign cysts. They reported that the SPINK1 level was higher in malignant/potentially malignant than in benign cystic pancreatic lesions (1609 ± 418 *vs* 46 ± 21 ug/L; $P = 0.0001$). These findings matched our study that showed that SPINK1 level was higher in malignant/potentially malignant cysts than in benign ones (0.91 *vs* 0.47, $P = 0.001$) with a sensitivity and specificity of 70.59% and 65.33%, respectively (Table 8).

In our study, mural nodules, cyst diameter, lymph node enlargement, mucin stain, CF CEA, SPINK1, and glucose measurements in CF were highly predictive of malignancy in univariate analysis. In comparison, only mural nodules, mucin stain, and SPINK1 were highly predictive of malignancy in multivariate analysis.

Of all these markers measured in CF, CEA, glucose, and SPINK1 were independent predictors of malignancy, suggesting that these markers could help differentiate potentially malignant cysts from benign cysts.

The analysis of recent markers - not investigated in this study – such as CF DNA is recommended for future research because it might add more diagnostic value in differentiating benign from malignant cysts.

CONCLUSION

Conclusion

EUS examination of cyst morphology with cytopathological and chemical analysis and CF analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 are valuable markers for predicting a malignant pancreatic cyst.

Recommendations

Further studies addressing new markers are recommended, which will provide a panel of laboratory data to recognize the malignant and potentially malignant lesions to establish a standard protocol for diagnosis and management. Also, CF DNA is considered a potential diagnostic agent with particular possible use in differentiating between benign and malignant cysts. Further investigation regarding this biomarker is recommended.

ARTICLE HIGHLIGHTS

Research background

Nowadays, the awareness of pancreatic cystic lesions has become an essential issue, especially with the increased incidence of asymptomatic pancreatic cysts in the general population. Therefore, the proper diagnosis, meticulous differentiation, and staging of these pancreatic cystic lesions (PCLs) are crucial for proper management and avoiding unnecessary treatment of benign lesions and missing early treatment of the malignant/pre-malignant lesions. Endoscopic ultrasound (EUS) examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the diagnostic capability. Also, many developed markers are valuable for predicting a malignant pancreatic cyst.

Research motivation

EUS examination of cyst morphology with cytopathological and chemical analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, carcinoembryonic antigen (CEA), glucose, and the serine protease inhibitor Kazal-type 1 (SPINK1) are valuable markers for predicting a malignant pancreatic cyst.

Research objectives

To evaluate the role of cyst fluid analysis of different tumor markers such as cancer antigens (*e.g.*, CA19-9 and CA72-4), carcinoembryonic antigen (CEA), SPINK1, interleukin 1 beta (IL-1β), vascular endothelial growth factor A (VEGF-A), prostaglandin E2 (PGE2), amylase, and mucin stain in diagnosing pancreatic cysts and differentiating malignant from benign lesions.

Research methods

This study included 76 patients diagnosed with PCLs using different imaging modalities. All patients underwent EUS and EUS-FNA for characterization and sampling of different PCLs.

Research results

The mean age of studied patients was 47.4 ± 11.4 years, with a slight female predominance (59.2%). Mucin stain showed high statistical significance in predicting malignancy with a sensitivity of 87.1% and specificity of 95.56%. It also showed a positive predictive value and negative predictive value of 93.1% and 91.49%, respectively ($P < 0.001$). We found that positive mucin stain, cyst fluid glucose, SPINK1, amylase, and CEA levels had high statistical significance ($P < 0.0001$). In contrast, IL-1β, CA 72-4, VEGF-A, VEGFR2, and PGE2 did not show any statistical significance. Univariate regression analysis for prediction of malignancy in PCLs showed a statistically significant positive correlation with mural nodules, lymph nodes, cyst diameter, mucin stain, and cyst fluid CEA. Meanwhile, logistic multivariable regression analysis proved that mural nodules, mucin stain, and SPINK1 were independent predictors of malignancy in PCLs.

Research conclusions

EUS examination of cyst morphology with cytopathological analysis and cyst fluid analysis could improve the differentiation between malignant and benign pancreatic cysts. Also, CEA, glucose, and SPINK1 could be used as promising markers to predict malignant pancreatic cysts.

Research perspectives

Further studies addressing new markers are recommended, which will provide a panel of laboratory data to recognize the malignant and potentially malignant lesions to establish a standard protocol for diagnosis and management. Also, cyst fluid DNA is considered a potential diagnostic agent with particular possible use in differentiating between benign and malignant cysts. Further investigation regarding this biomarker is recommended.

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FOOTNOTES

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REFERENCES

1 **Basturk O**, Coban I, Adsay NV. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med* 2009; **133**: 423-438 [PMID: 19260748 DOI: 10.5858/133.3.423]
2 **Jani N**, Bani Hani M, Schulick RD, Hruban RH, Cunningham SC. Diagnosis and management of cystic lesions of the pancreas. *Diagn Ther Endosc* 2011; **2011**: 478913 [PMID: 21904442 DOI: 10.1155/2011/478913]
3 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]
4 **Okasha H**, E Behiry M, Ramadan N, Ezzat R, Yamany A, El-Kholi S, Ahmed G. Endoscopic ultrasound-guided fine needle aspiration in diagnosis of cystic pancreatic lesions. *Arab J Gastroenterol* 2019; **20**: 86-90 [PMID: 31182342 DOI: 10.1016/j.ajg.2019.05.008]
5 **Boot C**. A review of pancreatic cyst fluid analysis in the differential diagnosis of pancreatic cyst lesions. *Ann Clin Biochem* 2014; **51**: 151-166 [PMID: 24097809 DOI: 10.1177/0004563213503819]
6 **Koito K**, Namieno T, Nagakawa T, Shyonai T, Hirokawa N, Morita K. Solitary cystic tumor of the pancreas: EUS-pathologic correlation. Gastrointest Endosc 1997; 45(3): 268-276 [DOI: 10.1016/s0016-5107(97)70269-4]
7 **Sperti C**, Pasquali C, Guolo P, Polverosi R, Liessi G, Pedrazzoli S. Serum tumor markers and cyst fluid analysis are useful for the diagnosis of pancreatic cystic tumors. *Cancer* 1996; **78**: 237-243 [PMID: 8673998 DOI: 10.1002/(SICI)1097-0142(19960715)78:2<237::AID-CNCR8>3.0.CO;2-I]
8 **Lee KS**, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010; **105**: 2079-2084 [PMID: 20354507 DOI: 10.1038/ajg.2010.122]
9 **Polkowski M**, Larghi A, Weynand B, Boustière C, Giovannini M, Pujol B, Dumonceau JM; European Society of Gastrointestinal Endoscopy (ESGE). Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. *Endoscopy* 2012; **44**: 190-206 [PMID: 22180307 DOI: 10.1055/s-0031-1291543]
10 **Lennon AM**, Canto MI. Pancreatic Cysts - Part 2: Should We Be Less Cyst Centric? *Pancreas* 2017; **46**: 745-750 [PMID: 28609361 DOI: 10.1097/MPA.0000000000000841]
11 **Matthaei H**, Schulick RD, Hruban RH, Maitra A. Cystic precursors to invasive pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 141-150 [PMID: 21383670 DOI: 10.1038/nrgastro.2011.2]
12 **Machicado JD**, Koay EJ, Krishna SG. Radiomics for the Diagnosis and Differentiation of Pancreatic Cystic Lesions. *Diagnostics (Basel)* 2020; **10** [PMID: 32708348 DOI: 10.3390/diagnostics10070505]
13 **Brugge WR**. The use of EUS to diagnose cystic neoplasms of the pancreas. *Gastrointest Endosc* 2009; **69**: S203-S209 [PMID: 19179158 DOI: 10.1016/j.gie.2008.12.029]
14 **Barresi L**, Tarantino I, Granata A, Curcio G, Traina M. Pancreatic cystic lesions: How endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle. *World J Gastrointest Endosc* 2012; **4**: 247-259 [PMID: 22720127 DOI: 10.4253/wjge.v4.i6.247]
15 **Thiruvengadam N**, Park WG. Systematic Review of Pancreatic Cyst Fluid Biomarkers: The Path Forward. *Clin Transl Gastroenterol* 2015; **6**: e88 [PMID: 26065716 DOI: 10.1038/ctg.2015.17]
16 **Lee CJ**, Scheiman J, Anderson MA, Hines OJ, Reber HA, Farrell J, Kochman ML, Foley PJ, Drebin J, Oh YS, Ginsberg G, Ahmad N, Merchant NB, Isbell J, Parikh AA, Stokes JB, Bauer T, Adams RB, Simeone DM. Risk of malignancy in resected cystic tumors of the pancreas < or =3 cm in size: is it safe to observe asymptomatic patients? *J Gastrointest Surg* 2008; **12**: 234-242 [PMID: 18040749 DOI: 10.1007/s11605-007-0381-y]
17 **Sarr MG**, Carpenter HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, DiMagno EP. Clinical and pathologic

correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms? *Ann Surg* 2000; **231**: 205-212 [PMID: 10674612 DOI: 10.1097/00000658-200002000-00009]

18 **Sahani DV**, Saokar A, Hahn PF, Brugge WR, Fernandez-Del Castillo C. Pancreatic cysts 3 cm or smaller: how aggressive should treatment be? *Radiology* 2006; **238**: 912-919 [PMID: 16439566 DOI: 10.1148/radiol.2382041806]

19 **Okasha HH**, Ashry M, Imam HM, Ezzat R, Naguib M, Farag AH, Gemeie EH, Khattab HM. Role of endoscopic ultrasound-guided fine needle aspiration and ultrasound-guided fine-needle aspiration in diagnosis of cystic pancreatic lesions. *Endosc Ultrasound* 2015; **4**: 132-136 [PMID: 26020048 DOI: 10.4103/2303-9027.156742]

20 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794 DOI: 10.1053/j.gastro.2004.02.013]

21 **Gaddam S**, Ge PS, Keach JW, Mullady D, Fukami N, Edmundowicz SA, Azar RR, Shah RJ, Murad FM, Kushnir VM, Watson RR, Ghassemi KF, Sedarat A, Komanduri S, Jaiyeola DM, Brauer BC, Yen RD, Amateau SK, Hosford L, Hollander T, Donahue TR, Schulick RD, Edil BH, McCarter M, Gajdos C, Attwell A, Muthusamy VR, Early DS, Wani S. Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study. *Gastrointest Endosc* 2015; **82**: 1060-1069 [PMID: 26077458 DOI: 10.1016/j.gie.2015.04.040]

22 **Morris-Stiff G**, Lentz G, Chalikonda S, Johnson M, Biscotti C, Stevens T, Matthew Walsh R. Pancreatic cyst aspiration analysis for cystic neoplasms: mucin or carcinoembryonic antigen--which is better? *Surgery* 2010; **148**: 638-44; discussion 644 [PMID: 20797749 DOI: 10.1016/j.surg.2010.07.023]

23 **Park WG**, Wu M, Bowen R, Zheng M, Fitch WL, Pai RK, Wodziak D, Visser BC, Poultsides GA, Norton JA, Banerjee S, Chen AM, Friedland S, Scott BA, Pasricha PJ, Lowe AW, Peltz G. Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts: glucose and kynurenine. *Gastrointest Endosc* 2013; **78**: 295-302.e2 [PMID: 23566642 DOI: 10.1016/j.gie.2013.02.037]

24 **Zikos T**, Pham K, Bowen R, Chen AM, Banerjee S, Friedland S, Dua MM, Norton JA, Poultsides GA, Visser BC, Park WG. Cyst Fluid Glucose is Rapidly Feasible and Accurate in Diagnosing Mucinous Pancreatic Cysts. *Am J Gastroenterol* 2015; **110**: 909-914 [PMID: 25986360 DOI: 10.1038/ajg.2015.148]

25 **Carr RA**, Yip-Schneider MT, Simpson RE, Dolejs S, Schneider JG, Wu H, Ceppa EP, Park W, Schmidt CM. Pancreatic cyst fluid glucose: rapid, inexpensive, and accurate diagnosis of mucinous pancreatic cysts. *Surgery* 2018; **163**: 600-605 [PMID: 29241991 DOI: 10.1016/j.surg.2017.09.051]

26 **Räty S**, Sand J, Alfthan H, Haglund C, Nordback I. Cyst fluid tumor-associated trypsin inhibitor may be helpful in the differentiation of cystic pancreatic lesions. *J Gastrointest Surg* 2004; **8**: 569-574 [PMID: 15239993 DOI: 10.1016/j.gassur.2004.01.005]

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