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REVIEW

# Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of pancreatic cysts by combined cytopathology and cystic content analysis

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## Abstract

Recent advances in imaging technology have resulted in an increase in incidental discoveries of pancreatic cystic lesions. Pancreatic cysts comprise a wide variety of lesions and include non-neoplastic cysts and neoplastic cysts. Because some pancreatic cysts have more of a malignant potential than others, it is absolutely essential that an accurate diagnosis is rendered so that effective care can be given to each patient. In many centers, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has emerged as the modality of choice that enables one to distinguish between mucinous and non-mucinous lesion, diagnose malignancy and collect cyst fluid for further diagnostic studies, such as pancreatic enzyme levels, molecular analysis and other tumor biomarkers. The current review will focus on EUS-guided FNA and the cytological diagnosis for pancreatic cysts.

**Key words:** Pancreatic cyst; Endoscopic ultrasound; Fine needle aspiration; Diagnosis; Cystic fluid analysis; Cytology



**Core tip:** Pancreatic cysts comprise non-neoplastic cysts and neoplastic cysts. It is absolutely essential that an accurate diagnosis is rendered so that effective care can be given to each patient. In many centers, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has emerged as the modality of choice that enables one to distinguish between mucinous and non-mucinous lesion, diagnose malignancy and collect cyst fluid for further diagnostic studies, such as pancreatic enzyme levels, molecular analysis, and other tumor biomarkers. The current review will focus on EUS-guided FNA and the cytological diagnosis and new classification for pancreatic cysts.

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## INTRODUCTION

The overall prevalence for cystic lesions of the pancreas has been estimated to be no more than 1% of all pancreatic neoplasms[1]. However, the advent of high-resolution imaging modalities has led to the increased frequency of incidentally discovered pancreatic cysts. In the United States, a prevalence of incidental pancreatic cysts estimates about 2.6% to 13.5% of adults[2-4]. The increasing incidence of pancreatic cystic lesions has been directly linked to increasing age[5]. Pancreatic cystic lesions are also being detected sooner rather than later as reflected in the decreasing median sizes of pancreatic cysts both in the United States and in other countries[6]. Although a recent study suggests that only 2% of pancreatic cysts are malignant at diagnosis[7], the trend of increasing discovery of pancreatic cysts is significant because some types of pancreatic cystic lesions carry an augmented risk for malignant transformation.

Pancreatic cysts comprise a wide variety of lesions and include non-neoplastic cysts and neoplastic cysts. The classification and nomenclature of pancreatic cysts are very important for pathologic and clinical diagnosis. The non-neoplastic cysts include pseudocysts, retention cysts, lymphoepithelial cysts, benign epithelial cysts, and congenital cysts. Non-neoplastic cysts are believed to have low to no malignant potential. Neoplastic cysts are typically categorized as mucinous and non-mucinous based on the type of epithelium they possess[8]. The mucinous cysts consist of mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). The non-mucinous cysts include serous cystadenomas, solid pseudopapillary neoplasms (SPN), cystic pancreatic neuroendocrine tumors (PNET), cystic pancreatic ductal adenocarcinomas (PDA) and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), pancreatoblastoma, lymphomas, sarcomas, and metastatic tumors. The neoplastic cysts are categorized as being malignant (*i.e.*, PDA, PNET) or having malignant potential (*i.e.*, MCN, IPMN, SPN). Among mucinous subtypes of cysts, it has also been suggested that branch duct IPMN (BD-IPMN), while having malignant potential, may exhibit more indolent behavior compared to main duct-IPMN[9,10].

The management options for pancreatic cystic lesions are as varied as the lesions they are designed to diagnose and treat. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) is a major technique used in many institutions to sample pancreatic cystic lesions. As will be described in this review, there are multiple ways available to further study these lesions, including cytologic diagnosis and cystic content analysis by chemical and molecular tests. A new histologic classification system for pancreatic lesions has also been introduced to help clinicians and patients understand the malignant potential of each type of pancreatic lesion. Based on new diagnosis and classification of the cystic lesions, most patients need no further treatment. However, many patients require surveillance or other more invasive therapies (*i.e.*, surgical resection) depending upon the risk of malignant transformation. Hence, obtaining an accurate differential diagnosis is of utmost importance in properly managing these patients in such a way that minimizes risk of complications[11].

## EUS-GUIDED FNA SAMPLES FOR PANCREATIC CYSTS

### *Initial imaging studies*

The initial clinical workup for incidentally discovered pancreatic cysts involves the use of radiologic imaging to further characterize the lesion[12]. MRI with magnetic resonance cholangiopancreatography (MRCP) is the preferred method over pancreatic protocol multidetector (MD) CT because MRCP is able to evaluate the presence of septa, nodules, main-duct involvement, and branch duct involvement. In many cases, it is also able to accurately distinguish between mucinous and non-mucinous cysts[13,14]. Studies have also found that, within the proper clinical context, MRI and CT are capable of determining which pancreatic cystic lesions are more likely to be malignant[15,16]. This is especially true if the features pathognomonic for a given lesion are present. However, in many instances, the combined clinical and radiologic picture is unable to elucidate the type of lesion or its likelihood of harboring malignancy, thus making definitive treatment difficult to achieve. Much of this has to do with the fact that morphologic features of many pancreatic cystic lesions frequently overlap and can appear similar on imaging studies[17]. In this regard, cytologic diagnosis with EUS-FNA is a good means to arriving at a more definitive diagnosis.

### *EUS-FNA procedure for pancreatic cysts*

EUS-guided FNA is a safe procedure that employs the use of an image guidance system and an endoscope that is passed through the esophagus and into the stomach and/or duodenum. Because the importance of obtaining a good sample as well as adequate sample preparation cannot be overemphasized, many centers perform EUS-guided FNA in conjunction with rapid on-site evaluation (ROSE) by a cytopathologist or cytotechnologist. ROSE has been shown to improve the diagnostic yield of specimens and turnaround time obtained by EUS-guided FNA[18-21]. During ROSE, a cytopathologist or cytotechnologist screens air-dried smears that are first stained with rapid-Romanowsky method, such as Diff-Quik® and Hemacolor®, in order to

determine specimen adequacy and to give a preliminary diagnosis, if possible. The rest smears can be alcohol-fixed and stained with the Papanicolaou stain. Additional FNA samples are collected in saline or other alcohol-rich preservative solutions for liquid-based preparations (*i.e.*, ThinPrep®, SurePath®), cytocentrifuge preparations, or cell blocks. Cell blocks are especially helpful in the event that immunohistochemistry is needed to differentiate between the different types of pancreatic lesions. Specimens obtained by EUS-guided FNA can also be used for further diagnostic studies, such as enzymatic testing and molecular testing (to be discussed below in detail in this review).

The advantages of EUS-guided FNA are numerous and include direct real-time visualization of the needle, identification of smaller lesions that can be missed by imaging studies, as well as identification of local metastases and invasion of structures[22]. One study recently showed that the incremental increase in diagnostic yield of EUS and fluid analysis over CT and MRI for prediction of a neoplastic cyst is 36% and 54%, respectively. Complication rates were also low, with pancreatitis being the most common complication (1.1%)[23]. One large prospective multicenter study revealed a complication rate of 6%; bleeding was the most common complication[24]. An extremely rare complication associated with EUS-guided FNA is tumor seeding, especially with IPMN[25-27].

Despite the high specificity of EUS-guided FNA, the main disadvantage that comes with EUS-guided FNA is that samples obtained are often hypocellular. The study by de Jong *et al*[28] showed that a cytopathologic diagnosis was only possible in one-third to one-half of all cases examined. However, it has also been suggested that the sensitivity, which can range from 60% to 100%, often depends upon an institution's experience with the technique[29]. One way to potentially overcome the low sensitivity of this procedure is to do cystic wall puncture (CWP), a procedure in which a targeted FNA of the cyst wall is performed after removal of cyst fluid. One study utilizing this method reported adequate cytologic material in 81% of all cases. Complication rate was minimal with only one patient developing mild pancreatitis post-CWP[30]. The study by Rogart *et al*[31] also showed that CWP may also be helpful in increasing the diagnostic yield of mucinous cystic lesions of the pancreas. Furthermore, there are some important diagnostic pitfalls. For example, GI contamination can cause one to interpret an inadequate specimen as adequate, thus leading to a false-negative diagnosis. Conversely, markedly reactive epithelial cells can be mistaken for malignancy[32,33]. Fortunately, it is possible to avoid these diagnostic pitfalls by making sure cytopathologists have a working knowledge of normal, reactive, and neoplastic pancreatic conditions as well as being sure to correlate all cytologic findings with each patient's clinical history and imaging studies.

## DIAGNOSIS OF PANCREATIC CYSTS BY CYTOLOGY

### *Standardized terminology and classification of pancreatic cysts*

Aspirates obtained from EUS-guided FNA are graded in much the same way as aspirates obtained for other non-gynecological specimens. Specimens that lack sufficient cytologic material to render a diagnosis are designated as "unsatisfactory". Specimens that have adequate cytologic material and that are helpful in explaining the presence of a radiologically detected lesion are designated as "satisfactory". Satisfactory specimens are further characterized as "negative for malignancy", "atypical", "benign neoplasm", "suspicious for malignancy" or "positive for malignancy" depending upon the degree of cytologic atypia, cellularity (or lack thereof) and other background features present. Wherever possible, more descriptive terms are also used if a specific pathologic diagnosis can be made. However, there is variable, if not conflicting terminology, used in different institutes and even by individual pathologists. Therefore, tremendous effort has been made to develop a standardized system of classification for pancreatic cytopathology. Recently, Pitman *et al*[34] published a "standardized terminology and nomenclature for pancreatobiliary cytology: The Papanicolaou Society of Cytopathology Guidelines" (see modified guideline in Table 1). In their categorization, "Non-Diagnostic" lesions are in Category I, lesions classified as "Negative for Malignancy" are in Category Ⅱ, "Atypical" lesions are in Category Ⅲ, lesions classified as "Suspicious for Malignancy" are in Category Ⅴ, and lesions that are "Malignant" are in Category Ⅵ. Category Ⅳ consists of Category ⅣA for "Neoplastic: Benign" and Category ⅣB for "Neoplastic: Other". Serous cystadenoma is the main neoplasm in Category ⅣA. In Category ⅣB, they include both mucinous neoplasms, such as IPMN and MCN, and non-mucinous neoplasms, such as pancreatic endocrine tumor. However, as detailed below, the morphologic, molecular, and immunohistochemical features are very different for these lesions, with mucinous neoplasms having a greater potential to become malignant than non-mucinous neoplasms. Therefore, we suggest that Category ⅣB should be further separated into Category ⅣB1 as "Neoplastic: Mucinous neoplasm" and Category ⅣB2 as "Neoplastic: Non-mucinous neoplasm". IPMN, MCN, and intraductal papillary neoplasm of the bile ducts should be included in Category ⅣB1, and pancreatic endocrine neoplasm, SPN, and the rare gastrointestinal stromal tumor should be in Category ⅣB2. Nevertheless, this classification system serves a significant step towards a much needed uniform categorization of these lesions. Ultimately, the authors hope that each category of pancreatic tumor will be further discussed with gastroenterologists, GI surgeons, and GI oncologists. The following section will

**Table 1 Pancreatic cytology terminology (modified from pitman *et al*[34], 2014)**

| Terminology category | Definition | Example interpretations |
|---|---|---|
| Category Ⅰ:<br>Non-diagnostic | No diagnostic or useful information about the solid or cystic lesion sampled | Gastrointestinal contamination only;<br>Non-specific cyst contents with insufficient cyst fluid volume for ancillary testing;<br>Evaluation limited by scant cellularity |
| Category Ⅱ:<br><br>Negative (for malignancy) | Adequate cellular and/or extracellular tissue to evaluate | Benign pancreatobiliary tissue in the setting of vague fullness and no discrete mass<br>Acute pancreatitis<br>Chronic pancreatitis<br>Autoimmune pancreatitis<br>Pseudocysts<br>Lymph epithelial cyst<br>Spleenful/accessory spleen |
| Category Ⅲ:<br>Atypical | Cells present with cytoplasmic, nuclear, or architectural features that are not consistent with normal or reactive cellular changes of the pancreas or bile ducts and are insufficient to classify them as a neoplasm or suspicious for a high-grade malignancy | Atypical ductal cells obscured by crush artifact<br>Scant population of small monomorphic polygonal cells of unclear origin: Normal cigar cells *vs* endocrine proliferation<br>Atypical bile duct epithelium with nuclear features suggestive of repair in a background of acute inflammation<br>Atypical bile duct epithelium with mucinous metaplasia and mild nuclear atypia |
| Category ⅣA:<br>Neoplastic: Benign | The presence of a cytological specimen sufficiently cellular and representative, with or without the context of clinical, imaging and ancillary studies, to be diagnostic of a benign neoplasm | Scant non-mucinous cuboidal epithelium and scant hemosiderin-laden macrophages in a non-mucinous cyst fluid consistent with the clinical impression of a serous cystadenoma |
| Category ⅣB1:<br><br>Neoplastic:<br><br>Mucinous neoplasm | Premalignant such as intraductal papillary neoplasm of the bile ducts (IPN-B), IPMN or MCN with low, intermediate or high-grade dysplasia by cytological criteria | MCN: Typically a multiloculated, mucin-producing epithelial neoplasm with sub epithelial ovarian-type stroma that in almost all cases does not communicate with the pancreatic ductal system and in almost all cases occurs in women; located in the body or tail; easily removed comparing life-long surveillance<br>IPMN: Primarily intraductal proliferations of ductal epithelium creating a macroscopic lesion resulting in ductal dilatation, cyst formation and/or a mass lesion<br>1 Main-duct IPMN: Associated with diffuse dilatation of any portion of the main pancreatic duct or the entire pancreas<br>2 BD-IPMN: Cysts adjacent to a non-dilated main pancreatic duct<br>IPN-B: A papillary proliferation of mucin containing neoplastic cells that may occur anywhere in the ductal system; similar to IPMN |
| Category ⅣB2:<br><br>Neoplastic:<br><br>Non-mucinous neoplasm | A low-grade malignant neoplasm such as well-differentiated PanNET, SPN or rare GIST | PanNET (pancreatic endocrine tumor and pancreatic endocrine neoplasm): A well-differentiated proliferation of the pancreatic endocrine cells creating a mass lesion greater than 0.5 cm that may or may not be functional by producing inappropriate levels of various hormones and that may or may not demonstrate aggressive features on histological examination<br>SPN: A solid, secondarily cystic low-grade epithelial neoplasm with established clonal mutations in cancer-associated genes and an ability to metastasize<br>GIST: Spindle cell and/or epithelioid mesenchymal neoplasms with differentiation along the lines of the interstitial cell of Cajal that usually expression c-kit protein (CD117), DOG1 and CD34 by immunohistochemistry; located in a peripanreatic location |
| Category Ⅴ:<br>Suspicious (for malignancy) | when some, but an insufficient number of the typical features of a specific malignant neoplasm are present, mainly pancreatic adenocarcinoma | Rare markedly atypical epithelial cells suspicious for adenocarcinoma<br>Mucinous cyst with high-grade epithelial atypia and abundant coagulate necrosis suspicious for invasive carcinoma<br>Solid cellular neoplasm with features suspicious for acinar cell carcinoma. Tissue for confirmatory ancillary studies is not available |
| Category ⅥA:<br><br>PDAC and variants | A group of neoplasms that unequivocally display malignant cytological characteristics and include PDAC and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), pancreatoblastoma, lymphomas, sarcomas and metastases to the pancreas | PDAC: A malignant invasive gland (duct) forming epithelial neoplasm typically composed of classic tubular glands; 85%-90% of all pancreatic malignancies<br>Colloid carcinoma (mucinous, non-cystic): Abundant extracellular mucin production, with at least 80% of the tumor on histology demonstrating large pools of extracellular mucin and cuboidal epithelial cells "floating" in the mucin |

| | | |
|---|---|---|
| | | Medullary carcinoma: Poor histologic differentiation, syncytial growth pattern, pushing borders and an intense lymphoplasmacytic response<br>Undifferentiated carcinoma with osteoclast-like giant cells: Distinctive type of sarcomatoid carcinoma with the striking and unique cytohistologic features characterized by a prominent component of reactive osteoclast-like giant cells in a background of spindle cells.<br>Undifferentiated carcinoma: A high-grade carcinoma composed of large, undifferentiated, markedly pleomorphic cells; 2%-7% of PDAC |
| Category ⅥA:<br><br><br><br>Malignancy:<br><br>Others | A group of neoplasms that unequivocally display malignant cytologic characteristics excluding PDAC and its variants; including acinar cell carcinoma, high-grade neuroendocrine carcinoma (small cell and large cell), cholangiocarcinoma, pancreatoblastoma, lymphomas, sarcomas and metastases to the pancreas | Cholangiocarcinoma: The diagnostic criteria for invasive cholangiocarcinoma are the same as for ductal adenocarcinoma; usually diagnosis by bile duct brushings with high false negative rate due to overlying benign epithelium, insufficient sampling, reactive change with stent; degeneration due to bile<br>Acinar cell carcinoma: A rare malignant epithelial neoplasm with exocrine acinar differentiation<br>Poorly-differentiated neuroendocrine carcinoma (small cell carcinoma or large cell neuroendocrine carcinoma): Rare high-grade neuroendocrine tumor with < 1% of pancreatic tumor and 2%-3% of PanNETs<br>Pancreatoblastoma: A rare neoplasm, primarily of childhood, characterized by acinar differentiation, endocrine differentiation and distinctive squamoid nests<br>Non-Hodgkin lymphoma: Rare and usually involve the pancreas secondarily<br>Metastatic tumors: Secondary neoplasms involving the pancreas are rare; most common: Renal cell carcinoma |

MCN: Mucinous cystic neoplasms; IPN-B: Intraductal papillary neoplasm of the bile ducts; IPMN: Intraductal papillary mucinous neoplasm; cPanNET: Pancreatic neuroendocrine tumor; SPN: Solid pseudopapillary neoplasms; PDAC: Pancreatic ductal adenocarcinomas.

now describe the cytologic features of some of the more common pancreatic cystic lesions in accordance with the current classification described by Pitman *et al*[34].

**Pseudo cyst (category Ⅱ: Negative):** Pseudocysts are the most common type of pancreatic cysts, accounting for at least 75% of all pancreatic cystic lesions. They generally arise in the setting of acute pancreatitis and are due to autodigestion of the pancreatic parenchyma. By definition, pseudocysts lack an epithelial lining and are instead composed of an inflammatory, fibrous capsule surrounding a region of necrosis. Aspirates are typically paucicellular and consist of granular debris, hemosiderin-laden macrophages, and bile (Figure 1A).

**Lymphangiomas and lymphoepithelial cysts (category Ⅱ: Negative):** Lymphangiomas and lymphoepithelial cysts are both very rare benign lesions of the pancreas. The former is characterized cytologically by a uniform population of small, round lymphocytes accompanied by histiocytes, plasma cells, centrocytes, and centroblasts, whereas the latter is characterized by numerous anucleated squamous cells and amorphous debris with rare to no lymphocytes present. Aspirates from lymphangiomas tend to be very cellular[35] (Figure 1B); however, aspirates from lymphoepithelial cysts are largely acellular. Although EUS-guided FNA may have a limited role in identifying lymphoepithelial cysts, it has been proposed that paying attention to signal intensity on MRI may be helpful in identifying these lesions preoperatively[36].

**Serous cystadenoma (category ⅣA: Neoplastic: benign):** Serous cystadenomas comprise 1% to 2% of all pancreatic neoplasms. There are two types that are named based on the number and size of its cysts. Serous microcystic adenomas, which are the more common of the two types, have numerous small cysts, whereas serous oligocystic adenomas have fewer but larger cysts. Serous cystadenomas occur most frequently in older women, with the preferred sites being the body and tail of the pancreas. Aspirates of serous cystadenomas are sparsely cellular and may contain rare fragments of flat sheets and/or loose clusters of cuboidal cells with glycogenated cytoplasm and indistinct cytoplasmic borders (Figure 1C).

**Mucinous neoplasm (category ⅣB: Neoplastic: others):** There are two distinctive types of mucinous tumors, namely MCN and IPMN. Because both of these entities share many morphologic features, it is almost impossible to tell the difference between the two based on cytomorphologic features alone. In these cases, direct correlation with clinical and imaging studies is required. In general, MCNs occur almost exclusively in middle-aged women, with most being located in the body or tail of the pancreas. Of note, these lesions are closed cysts that do not communicate with the ductal system. A defining histologic feature of these lesions is the presence of ovarian-type stroma directly beneath mucinous epithelium that is positive for estrogen and progesterone receptors. On the other hand, IPMN is seen more commonly in men and are typically seen in the head of the pancreas. Unlike MCN, IPMN is radiologically shown to communicate with the ductal system (typically involving the main pancreatic duct)

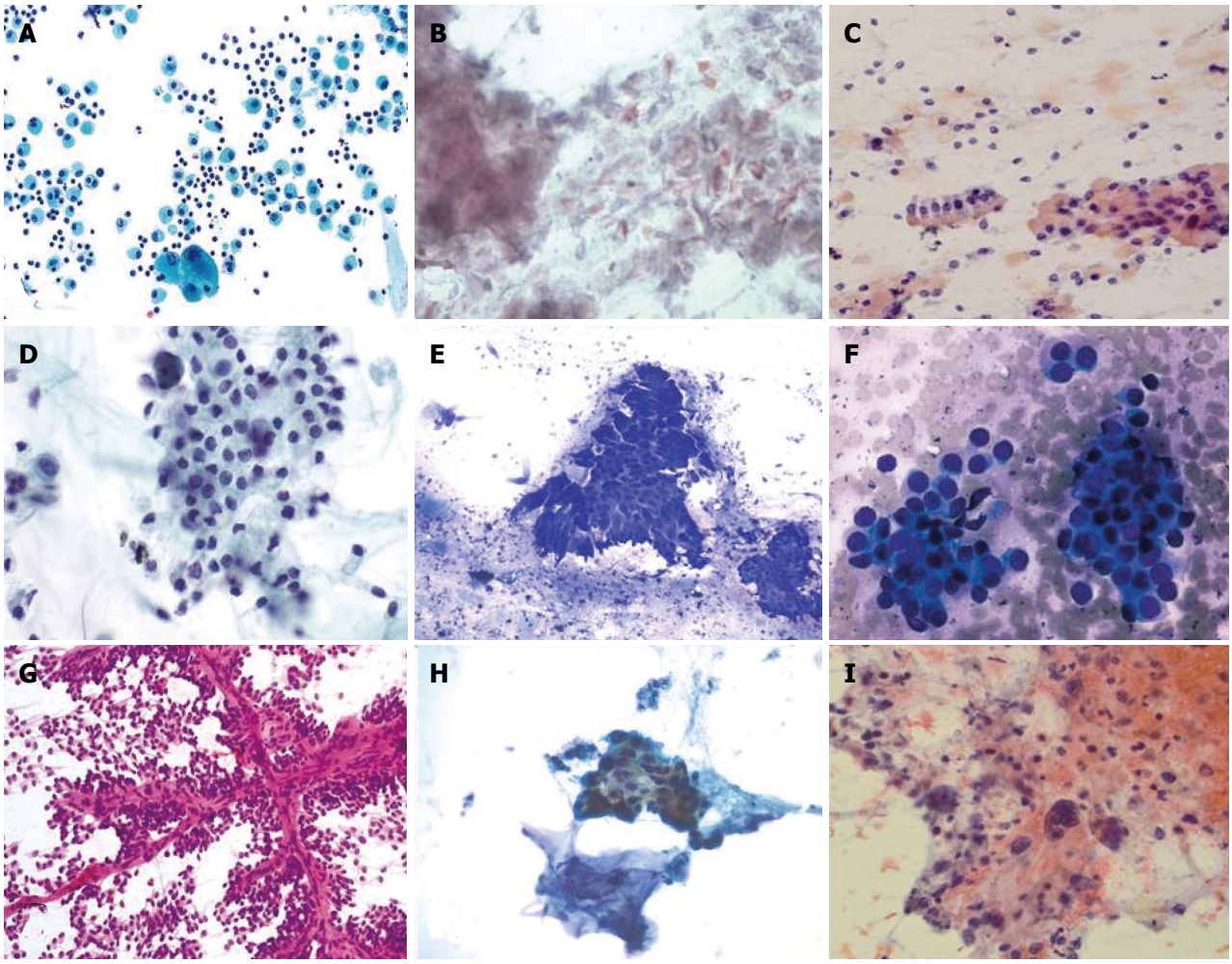


**Figure 1 Cytopathologic features of pancreatic cysts.** A: Pseudocyst: Notice the macrophages and inflammatory cells; epithelial cells are not seen; B: Lymphoepithelial cyst: Numerous anucleated squamous cells and keratinized debris are seen; C: Serous cystadenoma: One group of bland, monomorphic epithelial cells is present along with background histiocytes; D: Mucinous cystic neoplasm: A sheet of columnar cells with low-grad dysplasia in the background of mucin; E: Intraductal papillary neoplasm: Large papillary clusters are lined by tall, columnar cells containing intracytoplasmic mucin in the background extracellular mucin; F: Pancreatic neuroendocrine neoplasm: Bland, monomorphic epithelial cells with eccentrically placed nuclei arranged singly and in clusters characterizes this lesion; G: Solid pseudopapillary neoplasm: Notice the delicate, branching vessels and the poorly cohesive, bland epithelial cells; H: Pancreatic ductal adenocarcinoma with mucinous cyst: The ductal cells are arranged haphazardly and are characterized by hyperchromasia, nuclear pleomorphism and irregular nuclear contour; I: Undifferentiated carcinoma with osteoclast-like giant cells and mucinous cystic neoplasm: Multiple osteoclast-like giant cells and large haphazardly nucleus in the background of mucin.

and has the ability to grow along the entire length of the pancreatic duct and its branches. Aspirates of MCN and IPMN are hypocellular specimens that contain thick mucin and, if present, columnar mucinous sheets (Figure 1D and E). Cytologic interpretation is somewhat less problematic if nuclear and architectural atypia indicative of dysplasia or malignancy is identified. The WHO uses a three-tier classification based on degree of dysplasia present: benign, borderline, or malignant. Recent years, molecular tests such as KRAS and GNAS mutation are developed for differentiating MCN and IPMN. Nevertheless, given the malignant potential of these lesions, surgical resection is the most often utilized treatment of choice. Since cystic mucinous neoplasms have unique cytopathologic, molecular features and high risk for malignancy compared to non-mucinous neoplasms, we suggest that the Category Ⅳ B should be separated into two subcategories: Category ⅣB1: Neoplastic: Mucinous and ⅣB2: Neoplastic: Non-mucinous.

**Cystic PNET (category ⅣB: Neoplastic: others):** PNET represent approximately 1% to 2% of pancreatic neoplasms. Most PNET are small, functional solid tumors, but cystic pancreatic neuroendocrine tumors (cPanNETs) account for 13% to 17% of PanNETs[37]. PNET can secrete a variety of hormones, including insulin, glucagon, and somatostatin, and adrenocorticotrophic hormone. Although they can occur in any age group, they most commonly occur in adults. Aspirates of well-differentiated PNETs can range from sparsely cellular to highly cellular specimens consisting predominantly of abundant isolated cells and numerous bare nuclei. However, loosely cohesive clusters of cells and pseu-

dorosette formation are not uncommon. The cells are characterized by uniformly round, eccentrically placed nuclei with "salt-and-pepper" chromatin and moderate amounts of cytoplasm (Figure 1F). More poorly differentiated PNETs display more nuclear pleomorphic and higher mitotic activity. In doubtful cases, immunohistochemical stains for chromogranin and synaptophysin can be extremely helpful in confirming the diagnosis if the cell block is available. The surgical resection is the first line treatment. Enucleation or cytoreductive surgery is also recommended for patients with locoregional recurrences or hepatic metastases. Regional adjuvants such as radiofrequency ablation, transarterial chemoembolization, and others are often employed in an attempt to palliate symptoms and prolong survival[38]. Again, because cystic PNETs can be both functional and non-functional tumors with special morphological and immunohistochemical features, it should be separated from MCN into category IVB2: Neoplastic: Non-mucinous.

**SPN (category ⅣB: Neoplastic: others):** SPN are uncommon tumors of unknown malignant potential that predominantly occur in young women. Aspirates of these lesions are highly cellular, with the most characteristic features being myxoid or hyalinized vascular stalks lined by single or multiple layers of cells exhibiting round to oval nuclei, nuclear grooves, and indistinct cell borders (Figure 1G). Immunostain for β-catenin with nuclear positivity has emerged as a helpful attribute in diagnosing SPN. Other immunohistochemical stains that are helpful in confirming the diagnosis include CD10, CD56, vimentin and SMAD4. Surgical resection of these tumors leads to a good prognosis. With the special morphological features and immunohistochemical features of these lesions, SPN should be classified as Category ⅣB2: Neoplastic: non-mucinous.

**Pancreatic ductal adenocarcinoma with cystic neoplasm (Category Ⅵ: Malignant):** Pancreatic ductal adenocarcinomas (PDAC) with cystic neoplasm is the most common malignant cystic neoplasm of the pancreas and usually arises from MCN and IPMN. PDAC typically occur in older individuals, with smoking and alcohol abuse being major risk factors. Despite being able to detect these lesions at earlier stages, long term survival remains abysmal, with 90% of all patients dying within one year of diagnosis. Cytologically, aspirates are usually very cellular and consist of atypical ductal cells with irregular nuclear contours and prominent, centrally placed nucleoli arranged singly or in clusters and sheets (Figure 1H). Mitotic figures can also be seen.

### *Sensitivity and specificity of cytology based EUS-guided FNA*

Although it has been established that EUS-guided FNA has a valuable role in the multidisciplinary approach to the management of pancreatic cystic lesions, much controversy remains in regards to its ability to accurately triage patients with incidentally discovered lesions that appear benign on imaging. In one of the early studies performed by Frossard *et al*[39] in 2003, it was determined that EUS-guided FNA successfully identified the lesion of interest in 65 cases (97%). The overall sensitivity, specificity, positive predictive value, and negative predictive value for EUS-guided FNA in this study were 97%, 100%, 100%, and 95%, respectively[39]. The cytologic diagnosis of cystic lesions with EUS-FNA has been studied extensively with widely variable sensitivity[40-44]. The sensitivity has been reported to range from 23% to 100% and specificity has been reported to range from 71% to 100%[40,45,46]. One meta-analysis showed that the pooled sensitivity and specificity in diagnosing mucinous cystic lesions were 63% and 88%, respectively, in 11 studies and 54% and 92%, respectively, in 4 prospective studies[45]. In one recently published meta-analysis study, the sensitivity and specificity of cytology was 0.42 and 0.99; the sensitivity and specificity of K-RAS was 0.39 and 0.95; and the sensitivity and specificity of the combined test of cytology and K-RAS was 0.71 and 0.88, respectively[47]. The sensitivity in our study (47%) was between two meta-analysis results[46]. We further studied the false negative rate of EUS-FNA, and we found that the false-negative rate (3%) caused by an interpretative error was significantly lower than that caused by a sampling error (23%) ($P$ = 0.003). This finding suggests that sampling error, rather than interpretative error by cytology, is a major cause of high false-negative rates. We further examined the false-negative rate for solid lesions and cystic lesions. The false-negative rate for cystic lesions was significantly higher than that for solid lesions (53% *vs* 15%; $P$ = 0.005). Recently, Rogart *et al*[31] reported that cyst wall puncture performed during FNA improved the diagnostic yield for mucinous cysts[31]. In addition, cytologic classification with high-grade epithelial atypia in cystic lesion FNA specimens demonstrated a higher prediction for malignancy and added value for the clinical evaluation of cystic lesions[42,48]. One study also found that certain factors, such as the identification of a solid component and performing more than one pass, resulted in significant increases in sensitivity (as high as 78%)[49]. In light of these issues with sensitivity, a newer series has suggested that EUS-guided FNA, when used in conjunction with other "screening" tests, contributes to a triple-negative screening test (*i.e.*, no high-risk stigmata, no worrisome features, and no high grade atypia on cytology) that has a negative predictive value for malignancy of 99%[50]. In general, EUS-guided FNA has a low sensitivity, but good specificity[45]. More sensitive and specific techniques are needed and should be developed as new technologies emerge, such as cystic fluid analysis by chemical or molecular tests and confocal laser endomicroscopy.

Recently, cystic PNET diagnosis and management received a lot of attention. In one study, cytology made a specific diagnosis of a cystic PNET in 71% of the biopsies

compared with a specific diagnosis by EUS in 38% of cases[37]. All cysts but one revealed low carcinoembryonic antigen (CEA) levels (range, 0.2 to > 500 ng/mL; mean, 29.5 ng/mL), and amylase levels were < 500 U/L in all but 2 cases (range, 16-1493 U/L; mean, 205 U/L). In another study, cystic PNETs were found to be larger than solid PNETs (mean 26.8 mm *vs* 20.1 mm, $P = 0.05$) and more frequently nonfunctional (96% *vs* 80%, $P = 0.03$). With histology as the reference standard, EUS-FNA accuracies for malignancy of cystic and solid PNETs were 89.3% and 90%, respectively; cystic PNETs were less associated with metastatic adenopathy (22% *vs* 42%, $P = 0.03$) and liver metastasis (0% *vs* 26%, $P < 0.001$). Cystic fluid analysis ($n = 13$), showed benign cystic PNETs had low CEA, Ki-67 ⩽ 2%, and no loss of heterozygosity (LOH). Patients with cystic and solid PNETs had similar recurrence risk up to 5 years after complete resection[51]. In one review which compared EUS and EUS-FNA for cystic PNET, they found that EUS-FNA cytology and cyst fluid analysis is a useful adjunct to abdominal imaging in the diagnosis of pancreatic cystic lesions. They hypothesize that cyst fluid characteristics, including cytomorphological features, is the most accurate test to achieve a preoperative diagnosis and to provide a basis for prognostic prediction[52].

Another technique that shows promise in improving the sensitivity and specificity of detecting and diagnosing pancreatic cystic lesions is confocal laser endomicroscopy. Confocal laser endomicroscopy is a novel imaging technology in which a low-power laser illuminates and scans a single focal plane of the tissue[53-56]. This technique allows for the detection of the microscopic detail of the surface epithelium in pancreatic cysts. Needle-based confocal laser endomicroscopy (nCLE) utilizes a sub-millimeter probe that is compatible with an EUS needle and enables real-time imaging with microscopic detail of pancreatic cystic lesions[56]. The presence of epithelial villous structures based on nCLE was associated with pancreatic cystic neoplasm ($P = 0.004$) and provided a sensitivity of 59%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 50%. This technique is rather new for evaluating the pancreatic cystic lesions. However, we believe that the development of this new technique may facilitate sampling the most suspicious area of a cyst in the future.

## CYST FLUID ANALYSIS

As mentioned previously, pancreatic cystic neoplasms represent a diagnostic challenge for EUS-guided FNA because lining cells may or may not be adequately sampled, thus precluding further classification. The current way of solving this dilemma relies upon a combination of methods and includes visual cyst fluid evaluation at the time of immediate assessment, chemical analysis of cyst fluid, and molecular testing. All of these tests can be utilized to help to differentiate between mucinous and non-mucinous cysts.

### *Non-molecular methods*

The possibility of a mucinous cyst can be strongly suggested by looking for the "string sign". This can be assessed by stretching out a drop of cyst fluid between the thumb and index finger and subsequently measuring the length of the string of cyst fluid. A length of at least 3.5 mm is believed to be consistent with that of a mucinous cyst. Studies have also shown that mucinous cysts consistently have a higher relative viscosity compared to serum, whereas the opposite is true for non-mucinous cysts, which a lower relative viscosity compared to serum[57].

**Amylase:** The chemical analysis of cyst fluid relies upon examining pancreatic enzyme levels as well as the presence of tumor markers. Pancreatic enzyme levels are typically used to differentiate between pseudocysts and neoplastic cysts. One of the most important enzymes studied in making this distinction is amylase. Pseudocysts and other non-neoplastic cysts consistently show elevated levels of amylase. In fact, one study showed that an amylase level below 250 U/L virtually excludes pseudocysts from the differential diagnosis[58]. Conversely, amylase is low in neoplastic cysts.

**CEA:** A variety of tumor markers have been studied for their ability to discriminate between mucinous and non-mucinous cysts[57-60]. According to many studies, CEA levels are the most accurate[60,61]. Although CEA cutoff values of > 192 ng/mL have been shown to have an accuracy of 79%[60], levels > 800 ng/mL have been shown to be highly predictive of mucinous neoplasms with a specificity of 98%. Unfortunately, the sensitivity, even at these markedly elevated levels, is still less than 50%[58]. It is also important to note that CEA cannot be used to distinguish between benign and malignant lesions[62,63]. Amylase, however, may be helpful in this regard[64]. In contrast, a very low CEA level ⩽ 5 is 95% specific for pseudocysts, neuroendocrine tumors, and serous cystadenoma[58].

**Other markers:** Multiple biomarkers have also been studied to identify pancreatic ductal carcinoma (PDAC). Plectin-1, a marker related to PDAC, was found to be a potentially promising biomarker for the detection of malignancy in IPMNs[65]. Plectin-1 expression was assayed using immunohistochemistry in cyst fluid and tissue sample from benign and malignant IPMN, as well as lymph node metastasis from carcinoma arising from IPMN. The sensitivity and specificity were 84% and 83%, respectively. In animal models, Cathepsin E is specifically and highly expressed in PDAC and pancreatic intraepithelial neoplasias (PanINs), A prospective double-blind control study was performed to evaluate the accuracy of this method in diagnosing PDAC and PanINs of all grades (> 82.7%)[66].

### *Molecular methods*

**K-RAS mutation:** Molecular analysis of cyst fluid shows

**Table 2 Criteria for integrated molecular pathology diagnostic categories**

| Diagnostic category | Molecular criteria[1] | Co-existing concerning clinical features[2] |
|---|---|---|
| Benign | DNA lacks molecular criteria | Not considered for this diagnosis |
| Statistically indolent | DNA meets 1 molecular criterion | None |
| SHR | DNA meets 1 molecular criterion | 1 or more |
| Aggressive | DNA meets at least 2 molecular criteria | Not considered for this diagnosis |

[1]Four molecular criteria that have been independently correlated with pancreatic malignancy or high-grade dysplasia are used to make an integrated molecular pathology diagnosis: (1) a single high-clonality mutation; (2) elevated level of high-quality DNA; (3) multiple low-clonality mutations; and (4) a single low-clonality oncogene mutation; [2]Include any of the following: cyst size > 3 cm, growth rate > 3 mm/year, duct dilation > 1 cm, carcinoembryonic antigen level > 1000 ng/mL, cytologic evidence of high-grade dysplasia. (Table 2 from Al-Haddad *et al*[75] 2015 was permitted by publisher). SHR: Statistically higher risk.

promise in distinguishing not only between mucinous and non-mucinous cysts, but also in the diagnosis of malignant cysts. One study that examined surgically resected specimens showed that the identification of the K-RAS mutation had a sensitivity of 54% and a specificity of 100% for mucinous cysts. The combined used of CEA and K-RAS improved the sensitivity to 83% while decreasing the specificity to 85%[67]. However, a smaller study found that there was no increase in sensitivity when combining CEA and K-RAS[68]. LOH and increased DNA quantity have also been tried as a means of accurately predicting the presence of a mucinous lesion, but the sensitivity for each method is less than 11%. However, the detection of any molecular changes (*i.e.*, K-RAS mutation, LOH, or increased DNA quantity) has been found to be 90% specific for mucinous cysts[12]. Recently, one meta-analysis study found that the sensitivity and specificity of K-RAS was 0.39 and 0.95; and the sensitivity and specificity of the combined test of cytology and K-RAS was 0.71 and 0.88, respectively[47]. The K-RAS mutation combined with cytology test greatly increases the sensitivity of EUS-FNA. K-RAS mutation analysis may also prove to be a powerful ancillary for testing cystic samples with scant cellularity.

**GNAS mutation:** Another diagnostic marker that has received considerable interest is the presence of GNAS mutations. Recent studies have shown that GNAS mutations can be detected in IPMNs[69,70]. It has also been shown that the combination of GNAS and KRAS mutations in cyst fluid is very specific for IPMNs. One study found GNAS mutations to be significantly more prevalent in IPMNs (42%) than in SCAs (10%), adenocarcinomas (0%), and MCNs (0%). This same study also showed that double GNAS and KRAS mutations only occur in IPMNs ($P$ = 0.006) and that mutations in either gene equated to a sensitivity of 98% and a specificity of 84%[71]. GNAS mutations are rare to absent in MCN, SCA, PNET, or PDAC.

**MicroRNA change:** MicroRNA (miRNA) expression profiles have also received considerable interest and are currently being studied as another way to characterize pancreatic lesions. miRNA is nineteen to twenty-four nucleotide long single-stranded, non-coding regions of RNA that are highly stable and which may be useful in diagnosing various malignancies as well as pancreatic cystic neoplasms. In a recent study, together with IPMN surgical specimens, 65 cyst fluid samples were examined for differential selective miRNA candidate expression. A subset of 18 miRNAs separated high-grade from low-grade lesions. A logistic regression model using nine miRNAs allowed prediction of high-grade IPMNs, PNET and SPN *vs* low-grade IPMNs and SCA with a sensitivity of 89%, a specificity of 100% and area under ROC curve of 1[72]. Another study evaluated miRNA in 69 pathology specimens and identified several miRNA panels that enabled them to differentiate SCA from MCN and IPMN, and MCN from BD-IPMN with a sensitivity ranging from 85%-100% and a specificity of 100%[73].

**Integrated molecular pathology:** Perhaps the greatest dilemma in managing pancreatic cysts is the fact that none of the currently recommended guidelines can accurately predict the malignant potential of pancreatic cysts. For example, the current IAP 2012 criteria risk stratifies patients into two categories: "surveillance" criteria (low malignant potential) and "surgery" criteria (high malignant potential). Symptomatic patients with mucinous cysts and at least one other "high-risk stigmata" (*i.e.*, obstructive jaundice with a cyst located in the pancreatic head, a post-contrast enhancing solid component, a main pancreatic duct diameter $\geqslant$ 1 cm, abrupt change in duct caliber, cyst size $\geqslant$ 3 cm, presumptive diagnosis of MCN, and "suspicious" cytology) as detailed by the 2012 International Association of Pancreatology (IAP) guidelines should be referred for surgery[74]. Patients with cysts less than 1 cm and no concerning radiologic features can be monitored with periodic imaging studies. If more worrisome features are detected, the patients are subsequently referred for EUS-guided FNA to help determine the nature of the cyst (*i.e.*, mucinous versus non-mucinous) and whether malignancy is present. Nevertheless, given the high mortality rate for pancreatic cancer, the IAP ultimately recommends that any patient with "worrisome" features associated with malignancy undergo surgery. However, it has

been shown that approximately 60%-80% of patients undergoing surgery often have non-malignant disease. Therefore, other methods that prevent overtreatment of benign disease while providing early detection of cancer are needed.

Integrated molecular pathology (IMP) testing addresses this need it that incorporates all of the testing methods mentioned above (*i.e.*, cytology, imaging studies, fluid chemistry, and molecular analysis). Unlike other guidelines, it utilizes four different diagnostic categories of "benign", "statistically indolent", "statistically higher risk", or SHR, and "aggressive" based on both the number of molecular criterion met and other clinical features, if applicable (Table 2)[75]. In one study, 492 patients were categorized using IMP. Follow up for at least three years was available for 46% of patients. The overall accuracy was found to be 90%, and the specificity and negative predictive value were 91% and 97%, respectively. The sensitivity for malignant outcome with this cohort of patients was 83%, and the positive predictive value was 58%. When compared to the 2012 IAP criteria, it was found that the IAP criteria and IMP showed similar sensitivity and negative likelihood ratios. However, there was a statistically significant difference between the IAP guidelines and the IMP in that the specificity and positive likelihood ratios were higher using IMP criteria. These findings suggest that IMP is very useful in not only risk stratifying patients, but also in preventing patients with indolent disease from undergoing unnecessary surgeries[75].

## CONCLUSION

EUS-guided FNA serves a pivotal role in the accurate diagnosis of incidentally discovered pancreatic cysts. Its advantages over imaging alone include the ability to confirm the presence or absence of suspicious features identified on radiologic imaging, determine whether a lesion is malignant, and monitor for changes in cystic lesions. The new classification schema, while not perfect, goes hand-in-hand with the role of EUS-guided FNA in that it helps clinicians and patients to have a better understanding of which lesions need to be treated as opposed to those which do not, thus sparing patients from undergoing procedures that may result in increased morbidity and/or mortality. Despite these advantages, arriving at a proper diagnosis still requires the integrated use of clinical, radiologic, and cytological findings. Newer chemical and molecular studies show promise in improving the ability of clinicians to effectively diagnose and treat these lesions.

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REVIEW

# Imaging of common bile duct by linear endoscopic ultrasound

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## Abstract

Imaging of common bile duct (CBD) can be done by many techniques. Endoscopic retrograde cholangiopancreaticography is considered the gold standard for imaging of CBD. A standard technique of imaging of CBD by endoscopic ultrasound (EUS) has not been specifically described. The available descriptions mention different stations of imaging from the stomach and duodenum. The CBD lies closest to duodenum and choice of imaging may be restricted to duodenum for many operators. Generally most operators prefer multi station imaging during EUS and the choice of selecting the initial station varies from operator to operator. Detailed evaluation of CBD is frequently the main focus of imaging during EUS and in such situations multi station imaging with a high-resolution ultrasound scanner may provide useful information. Examination of the CBD is one of the primary indications for doing an EUS and it can be done from five stations: (1) the fundus of stomach; (2) body of stomach; (3) duodenal bulb; (4) descending duodenum; and (5) antrum. Following down the upper 1/3$^{rd}$ of CBD can do imaging of entire CBD from the liver window and following up the lower 1/3$^{rd}$ of CBD can do imaging of entire CBD from the pancreatic window. This article aims at simplifying the techniques of imaging of CBD by linear EUS.

**Key words:** Endoscopic ultrasound; Common bile duct; Pancreas; Pancreatic duct; Portal vein

**Core tip:** Endoscopic ultrasound (EUS) is a new technology which has a steep learning curve. It is difficult to learn EUS as the standard techniques of EUS imaging have not been established. The common description of every organ or structure has been done by a station-wise imaging by most of the authors. The imaging of common bile duct (CBD) is an important part of EUS examination. The techniques of imaging of CBD by EUS have not been defined so far. This article aims at simplifying the techniques of imaging of CBD by linear EUS.

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## INTRODUCTION

The common bile duct (CBD) can be imaged by many imaging modalities. Endoscopic ultrasound (EUS) is closest to endoscopic retrograde cholangio pancreaticography, which is the gold standard for imaging of CBD. A standard technique of imaging of CBD by EUS has not been specifically described and the available descriptions mention different stations of imaging from the stomach and duodenum[1-12]. Most operators prefer multi station imaging during EUS and the choice of selecting the initial station varies from operator to operator. The CBD lies closest to duodenum and choice of imaging may be restricted to duodenum for many operators where the imaging scanners do not allow deep image penetration. Detailed evaluation of CBD is frequently the main focus of imaging during EUS and in such situations multi station imaging with a high-resolution ultrasound scanner may provide useful information. In this article we review the techniques of linear imaging of CBD by EUS.

### *Applied anatomy of extra hepatic biliary tract*

The right and left hepatic ducts unite in the hilar plate close to the right end of porta hepatis in front of right branch of portal vein to form the common hepatic duct (CHD). The cystic duct (length, 3-4 cm) runs postero inferiorly and to the left from the neck of gall bladder to join the right border of CHD at an acute angle. The CBD is 6.0 to 8.0 cm long and is generally divided into supraduodenal (upper 1/3$^{rd}$), retroduodenal (middle 1/3$^{rd}$), retropancreatic (lower 1/3$^{rd}$) and intraduodenal segments. The supraduodenal CBD lies in the right border of lesser omentum (hepato-duodenal ligament) anterior to portal vein and to the left of hepatic artery proper[1]. The retroduodenal part passes behind the superior part of duodenum, to the right of gastroduodenal artery and in front of portal vein. The retropancreatic part runs behind the head of the pancreas to reach the medial border of second part of duodenum. In the retropancreatic course, CBD is intrapancreatic in 83% and retropancreatic in 17% cases[2]. The CBD and the main pancreatic duct (of Wirsung) unite to form the common channel (hepatopancreatic ampulla of Vater) which opens at the major duodenal papilla 8 cm distal to pylorus. The formation of a common channel occurs in 85% cases and in the rest 15% cases, the two ducts either open separately or form a V junction before opening.

### *Materials and methods*

All images in the present study have been generated from a detailed review of real-time recordings using the curved linear scanning echoendoscope EG-3830 UT (Pentax corporation, Tokyo, Japan), coupled with a Hitachi Avius and Hitachi 7500 processor (Hitachi Aloka Medical, Tokyo, Japan). Our image orientation is with the cranial aspect of the patient directed towards the right side of the screen. Four positions are commonly used during imaging from EUS: (1) the neutral position is where the front of the handle is facing the patient; (2) the open position to left is where the front of the handle is facing the patient's feet. It is reached by turning anti clockwise through 90° from the neutral position; (3) the open position to right is the opposite of the open position to left. It is reached by turning clockwise through 90° from the neutral position; and (4) a further 90° rotation from open position to right can bring the handle in a position opposite to the neutral position.

### *Stations of imaging*

EUS of the CBD can be done from five stations: (1) the fundus of stomach; (2) body of stomach; (3) duodenal bulb; (4) descending duodenum; and (5) antrum (Figure 1 and Table 1).

## MOVEMENTS DURING IMAGING

Rotation of the scope is the most important key to linear imaging of CBD. Rotation moves the imaging axis from one part of bile duct to other. Imaging with the scope in a straight position is helpful in transferring the effect of rotation of scope to the tip of ultrasound transducer. Most of the movements are done in a straight position of scope, except during imaging from station of duodenal bulb where the scope is placed in a J shaped position. Appropriate adjustments in right and left knobs along with in and out movement are also required to gain proper contact with the wall from all stations.

### *Imaging from fundus of stomach/OG junction*

Manipulation around/ just beyond OG junction (40 cm) should be done under vision to avoid perforation. The imaging around/just beyond OG junction is best started from an open left position but can be also tried from an open right position.

**Table 1 Common bile duct imaging from various stations during endoscopic ultrasound**

| Station | Home base structure | Main part of bile duct seen | Part of CBD seen on clockwise rotation[1] | Part of CBD seen anti clockwise rotation[2] |
|---|---|---|---|---|
| OG junction | l tributaries of LPV segment 2 and 3 | Segment 2 and 3 duct | Upper 1/3 | None |
| Body of stomach | Portal vein, splenic vein | Mid 1/3 | Lower 1/3 | Upper 1/3, left hepatic duct |
| Duodenal bulb | Portal vein | Mid 1/3 | Lower 1/3 | Upper 1/3 |
| Descending duodenum | SMV | Lower 1/3 | Mid 1/3, upper 1/3 | Intrapancreatic |
| Antrum | SMV | Lower 1/3 | Mid 1/3, upper 1/3 | None |

[1]Clockwise rotation needs to be combined with additional push in and out, and up and down movements; [2]Anti-clockwise rotation needs to be combined with additional push in and out, and up and down movements. Each of these positions brings the transducer closer to one of the four parts of CBD (upper 1/3, mid 1/3, lower 1/3 or intraduodenal) and the rest of CBD can be imaged by appropriate movement (clockwise or anti clockwise rotation, right or left movement or up and down movement). If mid 1/3 of CBD is identified in bulb an anti-clockwise rotation shows upper 1/3 CBD and clockwise rotation shows lower 1/3 of CBD. Similarly in stomach once mid 1/3 of CBD is identified clockwise rotation traces CBD towards lower 1/3 and anti-clockwise rotation traces CBD towards upper1/3. CBD: Common bile duct; SMV: Superior mesenteric vein; LPV: Left portal vein; OG: Oesophagogastric junction.

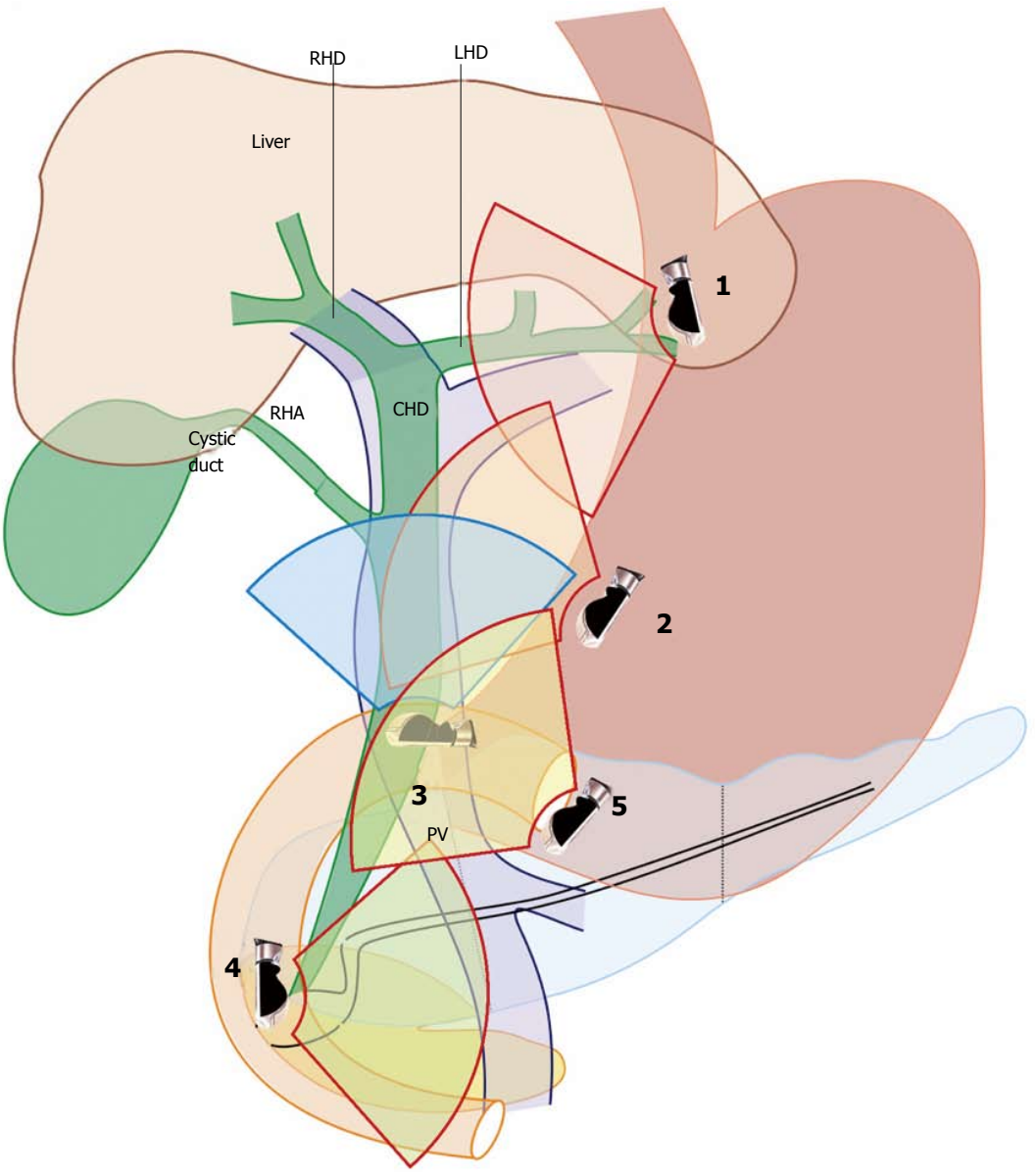


**Figure 1 Five positions of Common bile duct imaging by endoscopic ultrasound are shown.** CHD: Common hepatic duct; RHA: Right hepatic artery; RHD: Right hepatic duct; LHD: Left Hepatic duct.

**Imaging from open left position:** Clockwise rotation from an open left position follows the left lobe segment

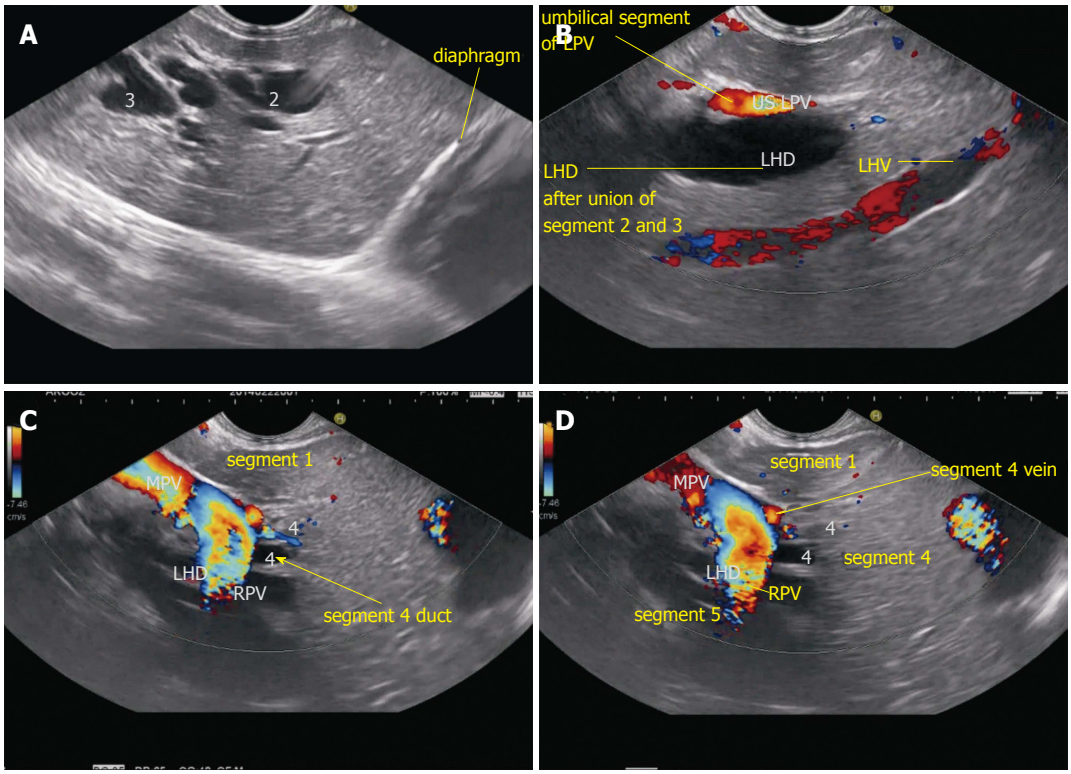


**Figure 2 Segmental ducts as seen on endoscopic ultrasound.** A: The dilated ducts of segment 2 and 3 ducts are seen in an open position to left; B: On clockwise rotation the segment 2 and 3 ducts fuse together in front of umbilical part of left portal vein. The left hepatic vein is also identified going from 2 o'clock position to 7 o'clock position; C: On further clockwise rotation the fused part of segment 2 and 3 ducts is joined by segment 4 duct from the cranial aspect (arrow) in front of the transverse segment of left portal vein; D: On further clockwise rotation the right portal vein is seen joining the left portal vein and the liver segment lying below the plane of right portal vein belongs to segment 5. RPV: Right portal vein; LPV: Left portal vein; LHD: Left hepatic duct; LHV: Left hepatic vein.

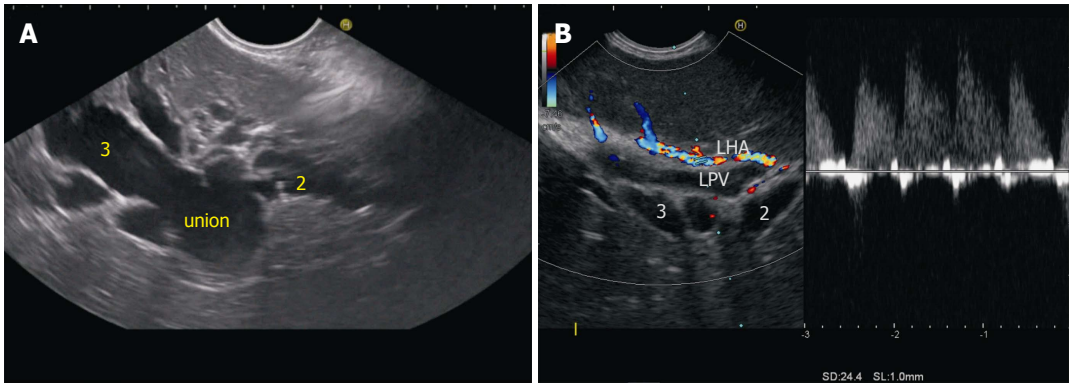


**Figure 3 Union of segmental ducts.** A: Segment 2 is identified as duct coming from cranial part of liver segment and segment 3 duct is identified as duct coming from caudal part of liver segment; B: Sometimes the ducts are not dilated and in such situation the tributaries of left portal vein can be identified after application of color doppler and followed to the union and formation of umbilical part of portal vein. LPV: Left portal vein; LHA: Left hepatic artery.

2 and 3 ducts to left hepatic duct and further rotation traces the left hepatic duct towards the liver hilum. If the intrahepatic biliary radicles (IHBR's) are dilated it is easy to follow the course of ducts by clockwise rotation. If the IHBR's are not dilated the segmental portal vein radicles should be followed. The gastrohepatic ligament (GHL), which come between the EUS probe and left lobe of liver, interferes with the imaging during rotation (Figures 2-4).

**Imaging from open right position:** Generally imaging of right lobe of liver is not possible from OG junction, as the right lobe ducts generally lies farther away from the probe. However the GHL does not interfere in imaging of right hepatic duct and with suitable adjustments of focus and frequency the right lobe and ducts of segment 4/5 (if dilated) can be identified and followed towards the upper CBD near the hilum by anti-clockwise rotation.

### *Imaging from body of stomach*

Following down the upper 1/3rd of CBD can do imaging

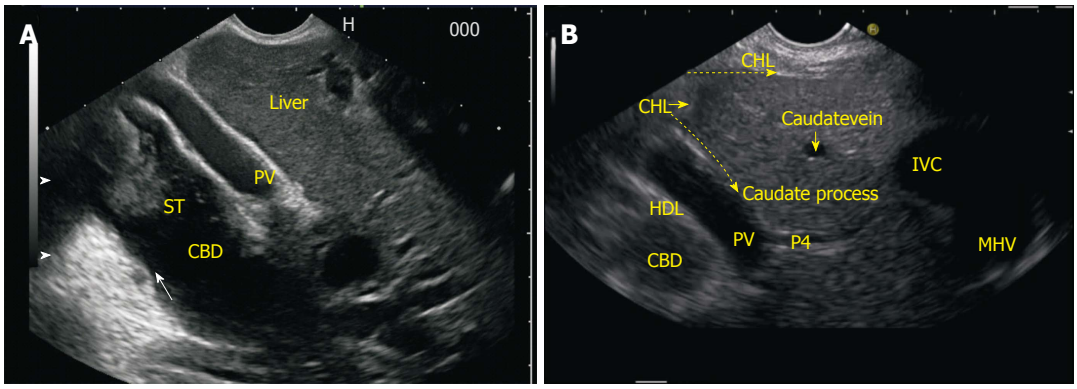


**Figure 4 Common bile duct as seen from the gastroesophageal junction.** A: A clockwise rotation moves the axis of imaging from an anterior position in stomach to a lateral position where the liver hilum is placed and follows the segmental duct towards the confluence of both the right and left hepatic ducts; B: In this figure the two limbs of GHL are seen. One of the limb runs on the under surface of liver and the other limb goes in the area between abdominal part of esophagus and liver. As the rotation is executed the presence of hyperchaotic GHL between esophagus and liver and the hepatoduodenal ligament near the liver hilum may interfere with imaging of part of the left or right hepatic ducts near the confluence. CHD: Common hepatic duct; IVC: Inferior venacava; HDL: Hepatoduodenal ligament; IVC: Inferior venacava; GHL: Gastrohepatic ligament.

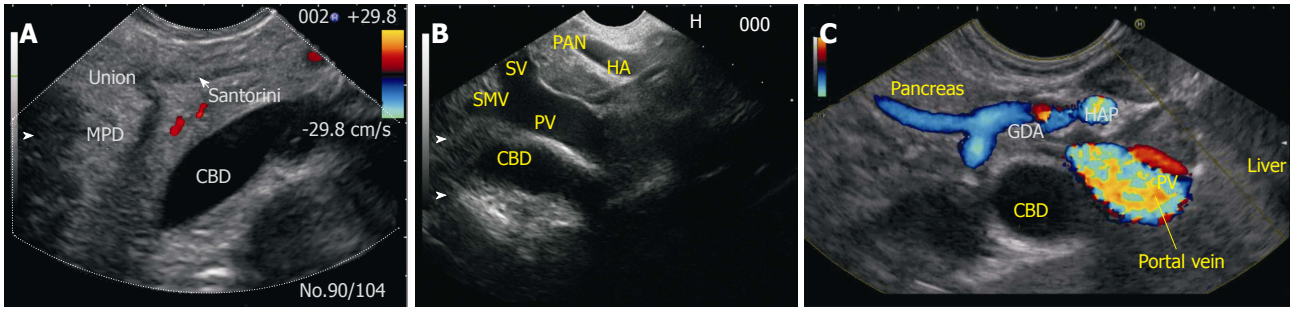


**Figure 5 Following down from upper 1/3.** A: A dilated bile duct can be easily followed down and push of the scope in a forward direction along with slight rotation changes the window of imaging from the liver window to pancreatic window. The parenchyma of head of pancreas provides an excellent window for visualization of dilated CBD. With experience even a non-dilated duct can be easily visualized from this position; B: When the probe comes to lie in fundus of stomach the stack of hepatic artery, portal vein and common bile duct can be seen through the liver window. In this picture the hepatic artery lies closest to the transducer, the portal vein lies on the undersurface of liver and the CBD is seen beyond the portal vein. The portal vein and the bile duct can be followed down towards the pancreas from the liver. The portal vein is followed down as SMV; C: When the probe comes to lie anterior to head of pancreas the stack of gastroduodenal artery, portal vein and bile duct can be seen with the help of the pancreatic window. CBD: Common bile duct; SV: Splenic vein; PV: Portal vein; HA: Hepatic artery; MPD: Main pancreatic duct; SMV: Superior mesenteric vein.

of entire CBD from the liver window and following up the lower 1/3rd of CBD can do imaging of entire CBD from the pancreatic window.

**Following down from liver window:** Imaging of CBD while following it down from the fundus towards body of stomach requires a movement of the EUS probe along lesser curvature. This movement can be easily executed under vision after distension of stomach with air but the presence of air usually creates interference with ultrasound imaging. To avoid this interference due to air, a smooth combination of three movements: (1) push in of about 25 to 30 cm. from fundus; (2) clockwise rotation of 90 degree; and (3) up movement of up and down knob for about 90 degree is generally preferred. This movement allows a relative blind slide of the transducer along lesser curvature with nil or minimum distension of air and follows down the CBD from upper 1/3rd towards the lower 1/3rd. Once the movement is completed the scope comes to lie in a position near the antrum and the left hand comes to lie close to the chest of the operator (Figure 5).

**Following up from pancreatic window:** A reversal of the movement described above can be done under vision by initially proceeding towards antrum after air inflation and subsequently coming back after air suction from antrum towards the fundus. This reversal movement follows up the CBD from the lower 1/3rd towards the upper 1/3rd. If it is difficult to trace the course of CBD by this movement, the home base of portal venous confluence of splenic vein with superior mesenteric vein is initially located in the neck of pancreas. The lower 1/3rd of CBD is easily identified behind the portal venous confluence (Figure 6).

### *Imaging from bulb*

The pylorus is located by "setting sun sign" and slight down angulation of tip may be required to get an end view of pylorus. Once the pylorus is seen the scope is

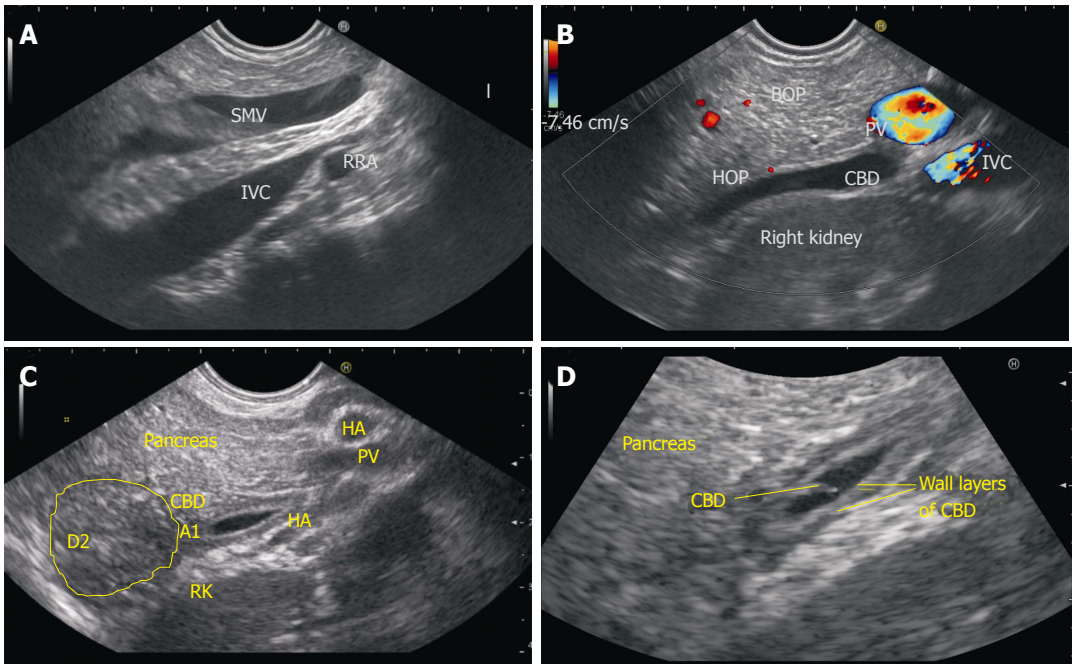


**Figure 6 Lower Common bile duct imaging from D2-D3.** A: In the hilum of liver the CBD lies anterior to the portal vein and both CBD and portal vein are positioned anterior to inferior vena cava. As the CBD is followed down towards ampulla the IVC remains goes posterior to head of pancreas whereas the SMV (followed down as a continuation of portal vein) comes to lie anterior to posterior part of head of pancreas. The CBD occupies the area of posterior part of head of pancreas between the SMV and IVC. This figure shows the typical appearance of SMV lying in front of IVC from stomach. If it is difficult to trace the course of CBD, the IVC, portal vein or superior mesenteric vein can be followed as a vascular home bases for tracing of CBD; B: In this figure the CBD is identified in posterior part of head of pancreas with slight anticlockwise rotation after visualizing the typical appearance of SMV lying in front of IVC; C: Once the Lower 1/3 of CBD is located it can be followed down towards the intrapancreatic part of CBD and zooming can help in imaging of papilla as well as 2$^{nd}$ part of duodenum; D: With selective zooming of bile duct the individual layers of bile duct can be identified. SMV: Superior mesenteric vein; CBD: Common bile duct; IVC: Inferior venacava; HOP: Head of pancreas; BOP: Body of pancreas; PV: Portal vein.

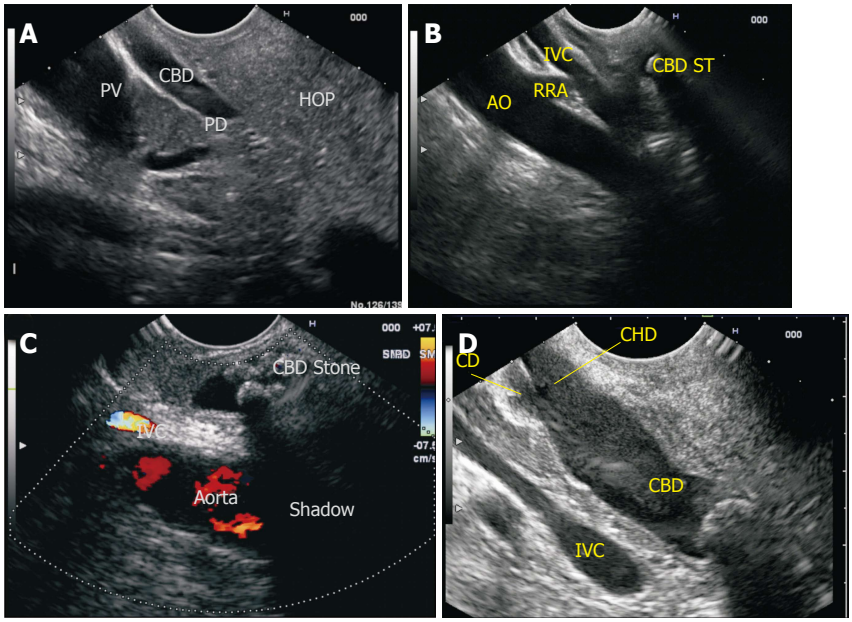


**Figure 7 Common bile duct Imaging from duodenal bulb.** A: The portal vein is identified as the home based position from duodenal bulb. From the home base position a limited range of movement of 90 degree to either side traces the entire CBD. A clockwise rotation traces the CBD towards the ampulla and identifies the middle and lower 1/3 of CBD and anticlockwise rotation traces the CBD towards the upper 1/3 and the GB/CD/CHD are also identified near the liver hilum. In this image the CBD is seen in a long axis for a long distance and the PD and portal vein are seen in a long axis for a short distance. This has been called as reverse stack sign; B: In this figure the stack of bile duct (with a stone) aorta and IVC is seen from duodenal bulb. The right renal artery is seen going behind the IVC. The CBD in this case lies in the retropancreatic part anterior to IVC; C: Two stones are seen in the path of acoustic shadow. Although both stones have same acoustic impedance yet it is the second stone, which is causing acoustic shadow. The second stone is surrounded by fluid and the sound waves go through acoustic medium of different acoustic impedance; D: The pyramidal shaped neck of pancreas and pancreatic duct are commonly identified between the probe and portal vein. CBD: Common bile duct; CHD: Common hepatic duct; IVC: Inferior venacava; PV: Portal vein; PD: Pancreatic duct; HOP: Head of pancreas; RRA: Right renal artery; AO: Aorta.

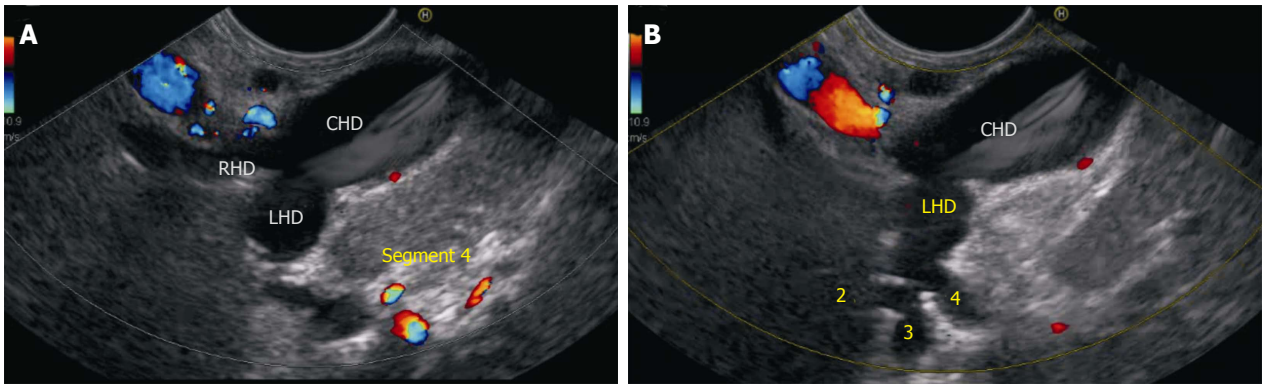


**Figure 8 Hilum imaging from duodenal bulb.** A: Imaging from duodenal bulb shows the proximity of CBD to the probe. The middle and upper 1/3rd of CBD and CHD dividing into RHD and LHD are seen. The RHD (average length 0.9 cm) and left hepatic duct (Average length 1.7 cm) unite in the hilar plate, close to the right end of porta in front of right branch of portal vein, to form the CHD; B: In this case it is possible to see the segmental ducts to segment 2, 3 and 4 through upper 1/3rd of CBD. CBD: Common bile duct; CHD: Common hepatic duct; RHD: Right hepatic duct; LHD: Left hepatic duct.

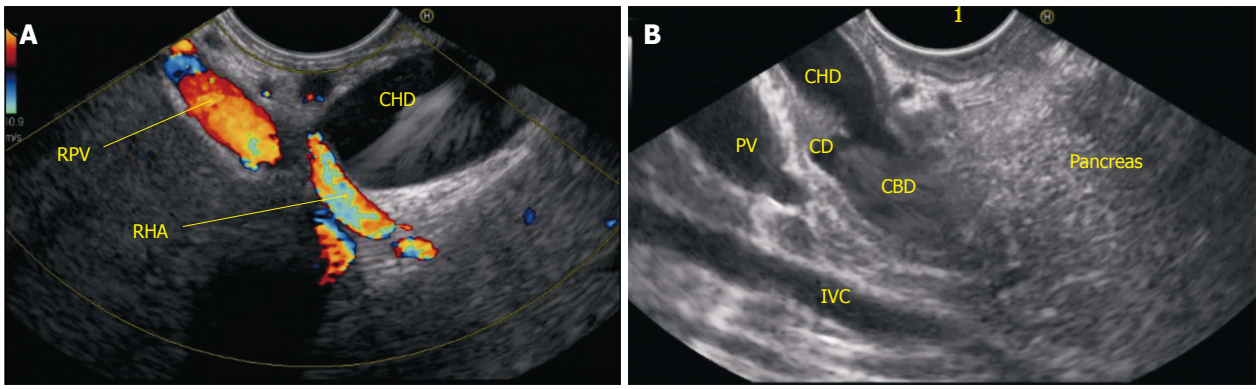


**Figure 9 Hepatocystic triangle seen from the duodenal bulb.** A: Imaging from duodenal bulb shows the relationship of right hepatic artery which goes behind the CHD to come and lie in the hepatocystic triangle; B: The bulb provides an opportunity to visualize the mid 1/3rd of CBD and usually provides an excellent window to see the division of CBD into CHD and CD. Most of the time the structure lying farther away from the screen is CD and can be traced towards the gall bladder. CBD: Common bile duct; CHD: Common hepatic duct; CD: Cystic duct; RPV: Right portal vein; RHA: Right hepatic artery; IVC: Inferior venacava.

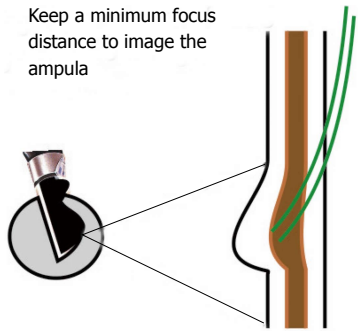


**Figure 10 Imaging of Common hepatic duct at papilla can be done after apposition of transducer with the papilla, which is the main endoscopic landmark.** It is appreciated as a thickening of the duodenal wall and a rounded 5-layered structure. Good views of papilla require three things: (1) transducer perpendicular to papilla; (2) good water coupling; (3) and motionless duodenum). If a balloon is used only a small amount of water should be filled in balloon to avoid smashing the delicate papilla. The imaging of papilla after instillation of about 50 to 100 mL water keeps the transducer away from papilla, increases the focal distance of imaging of transducer from papilla and places the papilla as well as lower 1/3 of CBD in the optimum focal distance of imaging (usually about 1 cm). CHD: Common hepatic duct.

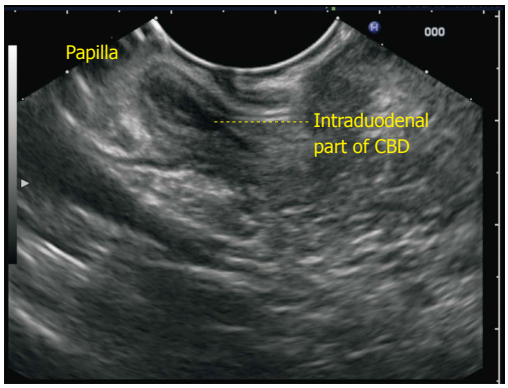


**Figure 11 The papilla is the protruding structure in the lumen of the duodenum and is covered on both sides by the muscular layer of the wall.** At the point of the entry of papilla into the duodenal bulb the continuity of muscular layer as a smooth duodenal fall is absent. At the point of union of bile duct and pancreatic duct the dilation of both ducts is named as ampulla. An attempt should be made to trace the intra papillary part of pancreatic duct all the way to the tip of the papilla or into a common ampulla. This can help in identifying the three patterns of opening of the bile duct and pancreatic duct, *i.e.*, common channel, V shaped or separate opening. CBD: Common bile duct.

pushed into 1st part of duodenum with slight upwards angulation and imaging from bulb is started after

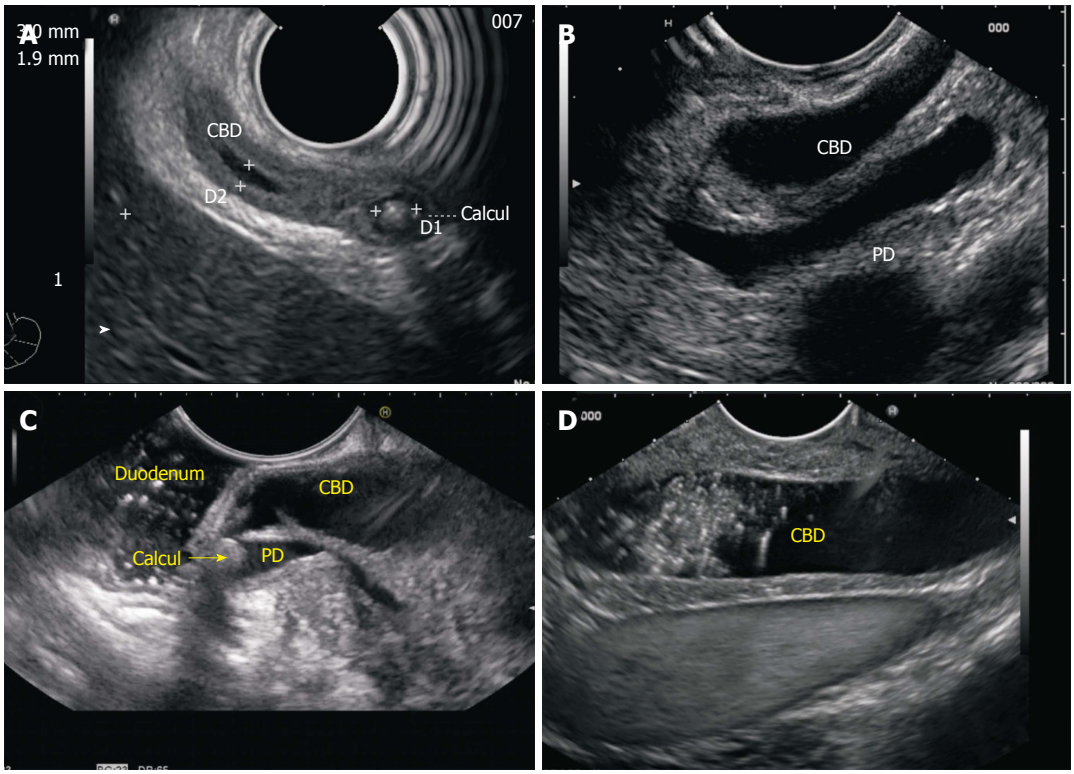


**Figure 12 Imaging from 2nd part of duodenum.** A: The intrapapillary part of CBD and the lower 1/3 of CBD is sometimes best visualized with the radial EUS scope as they provide a long axis of imaging of the entire bile duct in a long axis; B: However good view of CBD in a long axis can be also obtained by linear EUS scope. This image shows the dilated CBD and PD in a long axis in a case of periampullary carcinoma; C: The distended CBD may not provide room for good visualization as it comes very close to probe in a pathology involving papilla. This figure shows good view of CBD after instillation of 100 mL water which provides good coupling and also provides adequate focal distance. The stone is impacted in the common channel where it is also obstructing and dilating the pancreatic duct; D: The dilated CBD with sludge is seen from 2nd part of duodenum. On the far side of screen the IVC is also seen beyond the IVC. CHD: Common hepatic duct; EUS: Endoscopic ultrasound; IVC: Inferior venacava; CBD: Common bile duct; PD: Pancreatic duct.

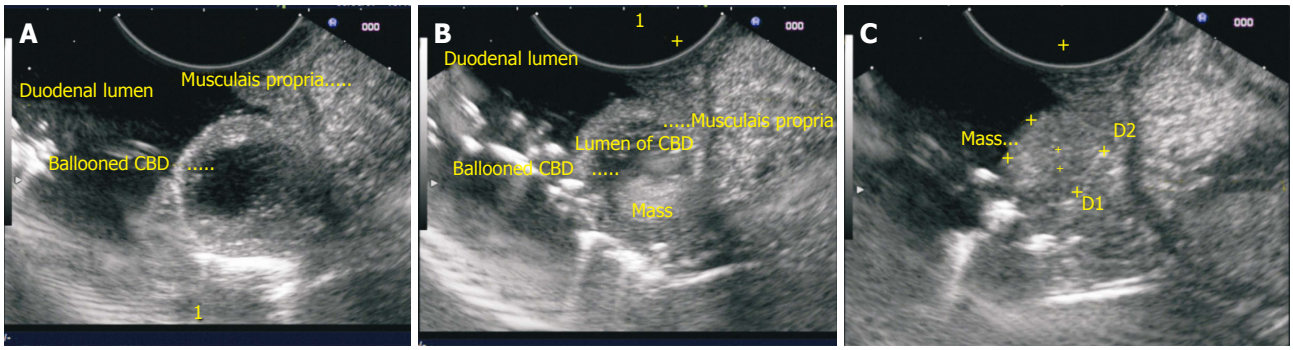


**Figure 13 Imaging of common hepatic duct from second part of duodenum.** A: A distended CBD is seen after good water coupling from 2nd part of duodenum but this image does not provide a clue to the diagnosis; B: An Ampulloma is seen within the distended intraduodenal part of bile duct; C: The tumor is seen within the intraduodenal part of CBD but it appears separate from the muscularis propria layer. CBD: Common bile duct.

establishing contact with posterior duodenal wall. The contact with wall is generally established by turning in an anticlockwise (ACW) direction with down angulation of up and down knobs. Sometimes in this imaging the ACW rotation of the scope may take the scope down and below the level of table in a straight scope position. With suitable rotation and minor adjustments of knobs a home base position is identified where the portal vein is seen on the far side of the screen going from 5 o' clock position to 11 o'clock position. In this home base position the middle 1/3rd of CBD is commonly identified with slight adjustments of right and left knobs between the transducer and portal vein. Clockwise rotation from this position traces the lower 1/3rd of CBD and ACW rotation traces the upper 1/3rd of CBD as well as the cystic duct and gall bladder (Figures 7-9).

### *Imaging from duodenum*

Imaging from duodenum requires two key movements. The first is entry into 2nd part of duodenum and the

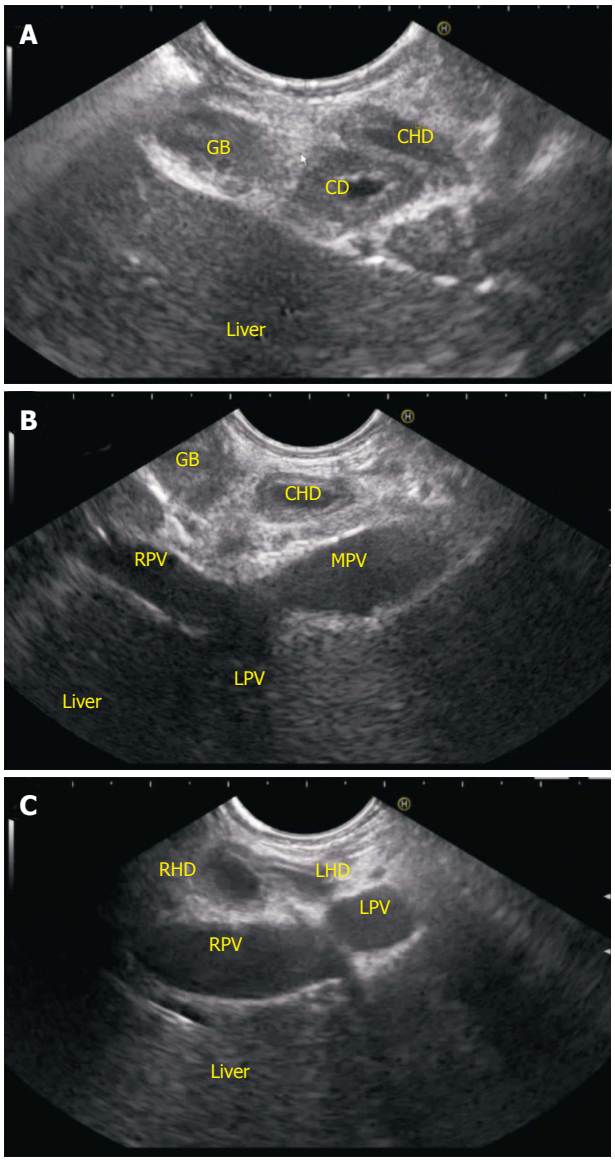


**Figure 14 Hilum imaging from D2.** A: Anticlockwise rotation from the 2nd part of duodenum traces the CBD towards the hilum. The cystic duct is seen taking origin from the aspect away from transducer and the gall bladder is visualized; B: When imaging is done from below upwards the imaging shows the CHD going towards the right portal vein; C: Further anticlockwise rotation towards hilum can show the left and right hepatic duct. The division of CHD into RHD and LHD occurs in front of right branch of portal vein. CBD: Common bile duct; CHD: Common hepatic duct; RHD: Right hepatic duct; LHD: Left hepatic duct; LPV: Left portal vein; RPV: Right portal vein.

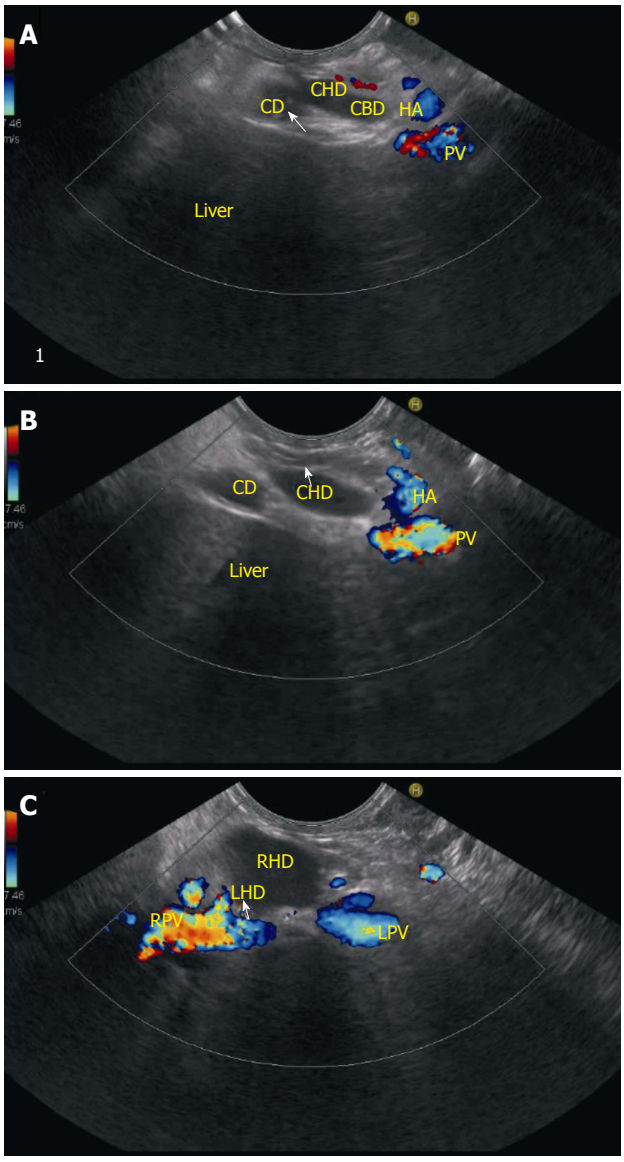


**Figure 15 Cystic duct and common hepatic duct imaging.** A and B: The cystic duct terminates at the right wall of the common hepatic duct in 85 to 90% of cases. In this case the CD is seen joining the right aspect of CHD; C: When the CHD is followed up it divides into right and left hepatic duct and this bifurcation generally lies in front of the right branch of the portal vein. As the echoendoscope is rotated counter clockwise the portal vein is followed up to its bifurcation and the RPV is seen on the right side of the screen. CHD: Common hepatic duct; CD: Cystic duct; CBD: Common bile duct; PV: Portal vein; HA: Hepatic artery; RHD: Right hepatic duct; LHD: Left Hepatic duct; LPV: Left portal vein; RPV: Right portal vein.

second is deep intubation into 3rd part of duodenum.

**Passage into D2:** Entry into D2 is facilitated by engagement of the tip of the probe at D1/D2 junction (superior duodenal angle). Four movements of knob at the superior duodenal angle, *i.e.*, "right turn of knob, up turn of knob, clockwise rotation of the scope and pulling back of the scope" help in passage of probe into second part of duodenum. These movements bring the scope in a short position and place the tip of scope near the papilla once the scope is shortened to about 55 cm. Slow pulling back for shortening can be done by pulling the shaft of scope with the use of right hand or by the use of outward pressure on the shaft of scope by ulnar aspect of the left hand in an open right position. Endoscopic view should be always maintained during a combination of these movements while shortening to avoid a sudden jerk and entry of the transducer into 2nd part of duodenum.

**Passage into D3:** Once the second part of duodenum is entered two to three times pushing in and out is required to position the scope deeper into the third part

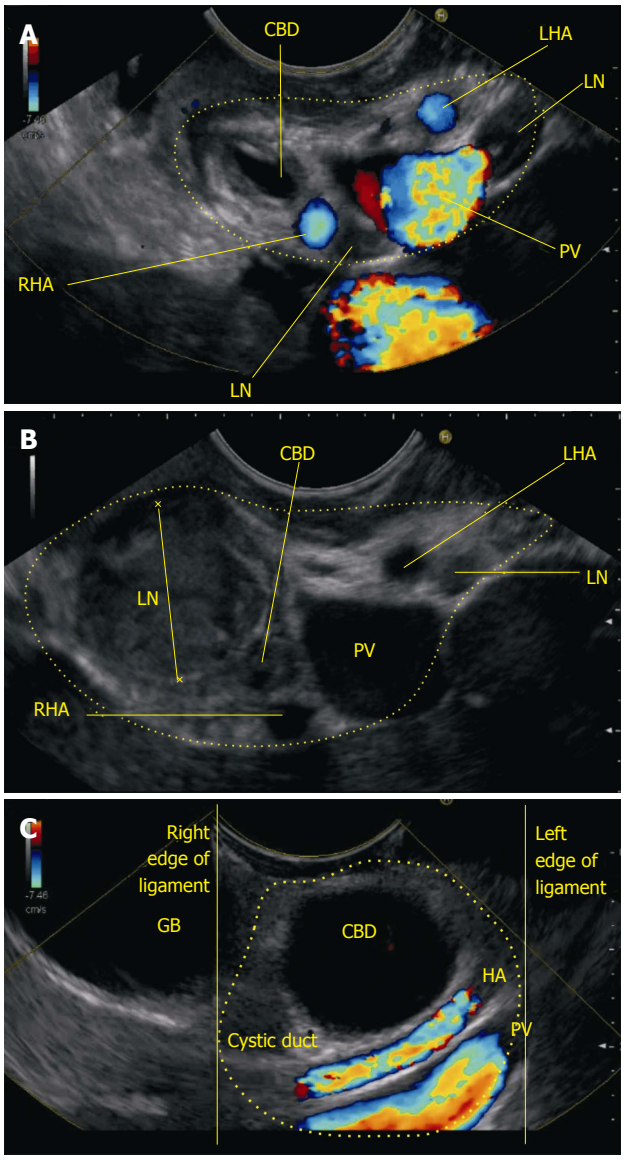


**Figure 16 Hepatoduodenal ligament.** A: The anticlockwise rotation takes the probe towards the hilum of liver the bile duct is demonstrated in a transverse axis. The HDL contains the structures of portal triad; B: Further anticlockwise rotation shows an abnormal lymph node within the hepatoduodenal ligament which is causing obstruction of CBD; C: On further anticlockwise rotation the probe moves towards the hilum of liver and the dilated bile duct is demonstrated in a transverse axis along with cystic duct and gall bladder. The portal vein and hepatic artery are demonstrated in long axis. All these structures shown lie in the hepatoduodenal ligament near the hilum except the gallbladder. CBD: Common bile duct; CHD: Common hepatic duct; RHA: Right hepatic artery; LHA: Left hepatic artery; LN: Lymph node; PV: Portal vein; HDL: Hepatoduodenal ligament.

of duodenum.

**Imaging from duodenum:** From the third part of duodenum a combination of three movements, *i.e.*, slow withdrawal up to the first part of duodenum, clockwise and ACW torque and upward movement of the up and down knobs is required for getting good views of lower 1/3$^{rd}$ of bile duct. This combined movement traces the CBD from the lower 1/3$^{rd}$ towards the upper 1/3$^{rd}$ but as the scope comes towards the first part of

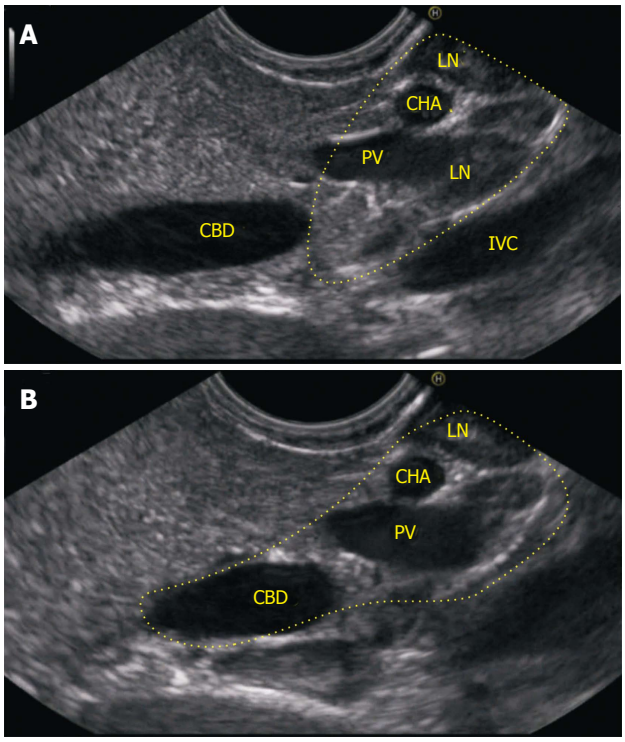


**Figure 17 When the scope comes to lie in antrum the splenic vein can be followed towards the portal venous confluence easily.** Once the portal venous confluence is identified a slight anticlockwise torque with push generally identifies the lower 1/3 of CBD in head of pancreas. Once the duct is identified the adjustment of focus, on the far side of screen with adjustment to lower frequency may be required for proper visualization of CBD behind the confluence. CBD: Common bile duct; LN: Lymph node; CHA: Common hepatic artery; PV: Portal vein; LN: Lymph node; IVC: Inferior venacava.

duodenum it tends to slip back into stomach. Movement of the up knob in a fully up position and maintaining a clockwise stance during slow torque from the 2$^{nd}$ part of duodenum helps in preventing the scope from slipping back. Wedging the scope at D1/D2 junction with an inflated balloon is an alternative, which is preferred by some operators to prevent slipping back, but carries a small disadvantage of reverse intussusception of the 2$^{nd}$ part of duodenum into stomach.

In a small number of cases it may be difficult to trace a normal CBD during this combined movement as most of the lumen of CBD gets compressed due to the pressure of transducer. In such cases the combined movement should be done with a main thrust on ACW rotation till it visualizes the anechoic bile duct within the bean shaped hepatoduodenal ligament. A clockwise rotation with slight push and relaxation of the pressure on up and down knob (reverse of the combined movement) now traces the CBD from the liver hilum towards the papilla.

Imaging of CBD should be done from below the papilla from the third part of duodenum after instillation of water whenever pathology of papilla (stone or a periampullary tumor) causes distension of intraduodenal part of CBD. This technique provides adequate focal distance for imaging of papilla and good water coupling

(Figures 10-16).

### *Imaging from antrum*

This imaging is similar to imaging through the pancreatic window from stomach as already described above. It can be done if evaluation of CBD is considered necessary once the scope slips back from the 2nd part of duodenum or once the examination from duodenum is completed. As the scope comes to lie opposite the head of pancreas the pancreatic window provides optimum imaging of lower 1/3rd of CBD (Figure 17).

## CONCLUSION

The techniques described in the above section can be expected to reproduce the images as discussed in majority of cases and from most of the stations. The only station of CBD imaging which may not reproduce the images as described is from duodenal bulb. This difference in reproducing the images and a great variability of images comes mainly due to the variability of the position of scope (short loop, or J shaped position) and due to the use of balloon (nestled, wedged, withdrawn wedged, intussuscepted). The basic concept of imaging however remains simple: stomach shows mainly the upper 1/3rd of CBD, bulb shows mainly the middle 1/3rd of CBD and duodenum shows mainly the lower 1/3rd of CBD. The follow up imaging to trace entire CBD requires a clockwise rotation and push from upper 1/3rd of CBD. The follow up imaging to trace entire CBD requires an ACW rotation and pull from lower 1/3rd of CBD. The follow up imaging to trace entire CBD requires a clockwise rotation to trace the lower 1/3rd and an ACW rotation to trace the upper 1/3rd when imaging is started from middle 1/3rd of CBD.

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# Reality named endoscopic ultrasound biliary drainage

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## Abstract

Endoscopic ultrasound (EUS) is used for diagnosis and evaluation of many diseases of the gastrointestinal (GI) tract. In the past, it was used to guide a cholangiography, but nowadays it emerges as a powerful therapeutic tool in biliary drainage. The aims of this review are: outline the rationale for endoscopic ultrasound-guided biliary drainage (EGBD); detail the procedural technique; evaluate the clinical outcomes and limitations of the method; and provide recommendations for the practicing clinician. In cases of failed endoscopic retrograde cholangiopancreatography (ERCP), patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. EGBD is an attractive alternative to PTBD or surgery when ERCP fails. EGBD can be performed at two locations: transhepatic or extrahepatic, and the stent can be inserted in an antegrade or retrograde fashion. The drainage route can be transluminal, duodenal or transpapillary, which, again, can be antegrade or retrograde [rendezvous (EUS-RV)]. Complications of all techniques combined include pneumoperitoneum, bleeding, bile leak/peritonitis and cholangitis. We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper GI tract anatomy, gastric outlet obstruction, a distorted ampulla or a periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

**Key words:** Endoscopic ultrasound; Rendezvous; Biliary drainage; Obstrutive cancer; Papillary obstrution



**Core tip:** In this minireview, we will discuss about endoscopic ultrasound-guided biliary drainage (EGBD) and new interesting endoscopic ultrasound therapeutic biliary methods. We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper gastrointestinal tract anatomy, gastric outlet obstruction, a distorted ampulla or periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

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## INTRODUCTION

Endoscopic ultrasound (EUS) is used for diagnosis and evaluation of many diseases of the gastrointestinal tract. In the past, it was used to guide a cholangiography[1], but nowadays it emerges as a powerful therapeutic tool in biliary drainage.

Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for drainage of an obstructed common bile duct (CBD) in patients with distal obstruction. Lower success rates are seen in patients with surgically altered anatomy and neoplastic diseases due to failure to access the duodenum or more difficult duct access[2]. However, EUS-guided biliary drainage (EGBD) may be a viable alternative to ERCP in patients with malignant distal CBD obstruction[3].

In 2001, Giovannini *et al*[4] performed the first palliative hepaticogastrostomy (HGS) under EUS guidance in a patient with inoperable hepatic hilar obstruction. Recently, experience from EUS-guided biliary duct drainage attempts at 6 international centers was reviewed and showed successful bile duct drainage for all techniques combined in 87% cases[5]. Although performed for almost two decades, during the last five years there was a substantial increase in this type of procedure. These publications suggest that EGBD can provide high levels of technical success with acceptable complication rates[6].

The indications for EGBD include: failed conventional ERCP; altered anatomy; tumor preventing access into the biliary tree; and contra-indication to percutaneous access[7].

If the papilla is accessible, a rendezvous technique (EUS-RV) can be adopted wherein EUS is used to puncture the bile duct and a wire is negotiated through the papilla and further therapy is carried out through ERCP. If the papilla is not accessible then EUS is used to access the bile duct and create a fistula for placement of a stent called the transmural technique[8].

The objectives of this review are: Outline the rationale for EGBD; detail the procedural technique; evaluate the clinical outcomes and limitations of the method; and provide recommendations for the practicing clinician.

## RATIONALE FOR USE EGBD

In cases of failed ERCP, patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. EGBD is an attractive alternative to PTBD or surgery when ERCP fails[9]. In a prospective single-center randomized study, EGBD and PTBD were compared in patients with unresectable malignant biliary obstruction. Technical success and clinical success were 100% in both groups. The complication rate for PTBD was 15.3% and the complication rate for EGBD was 25% ($P$ = 0.2), and the cost of the procedures was similar (7570 USD and 5573 USD respectively, $P$ = 0.39)[10]. The surgical bypass is an option only for patients who are good surgical candidates. Despite the more invasive approach, surgery produced better drainage.

ERCP may be challenging or may fail in certain situations, including post-surgical anatomy, periampullary diverticula, ampullary tumor invasion, and high-grade strictures. EUS-guided interventions may allow access or direct therapy in ERCP failures. In a retrospective single-center cohort study, if the primary intended EUS-guided anterograde cholangiopancreatography (EACP) intervention failed, crossover to other type of EACP therapy was performed, when clinically appropriate-in 95 of 2566 ERCP procedures (3.7%). EUS-guided cholangiography and pancreatography were successful in 97% and 100%, respectively (Figure 1). EUS-RV and ERCP was successful in 75% of biliary procedures and in 56% of pancreatic procedures. Direct EUS-guided therapy was successful in 86% and 75% of biliary and pancreatic procedures, respectively[11]. Another systematic review evaluated the efficacy of EGBD in patients with surgically altered anatomy with 74 cases included for analysis. The pooled technical success, clinical success, and complication rates of all reports with available data were 89.18%, 91.07% and 17.5%, respectively[12].

We recommend surgical bypass for patients with both duodenal and biliary obstructions who are good surgical candidates, but EGBD might be better than PTBD in patients with large volume ascites or patients who refuse external drainage[13].

A gallbladder biliary drainage is necessary in acute cholecystitis with poor performance status and septic shock patients. Jang *et al*[14] showed that EUS-guided naso-gallbladder drainage *via* transluminal technique is safe, effective and similar compared to percutaneous transhepatic gallbladder drainage, with a significant lower rate of postoperative pain (1 *vs* 5; $P$ < 0.001).

Others therapeutics modalities guided by EUS are transmural drainage of pancreatic pseudocysts[8], treatment of distal inflammatory biliary stricture[15], renal biopsy by fine neddle aspiration (EUS-FNA)[16], preoperative fine-needle tattooing insulinoma[17].

## PROCEDURAL TECHNIQUE

EGBD can be performed at two locations: transhepatic (TH), through segment Ⅲ, when the probe is placed at the stomach cardia and lesser curvature or jejunum (in altered anatomy) or extrahepatic (EH) when the needle access the CBD directly, either using the

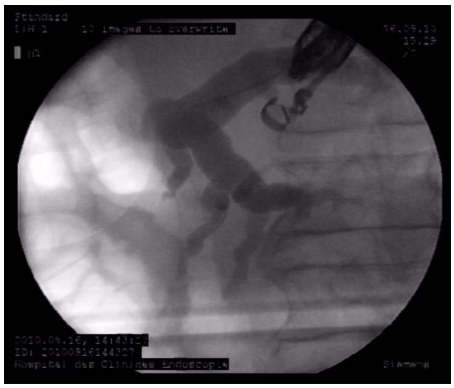

**Figure 1 Intra-hepatic cholangiography.**

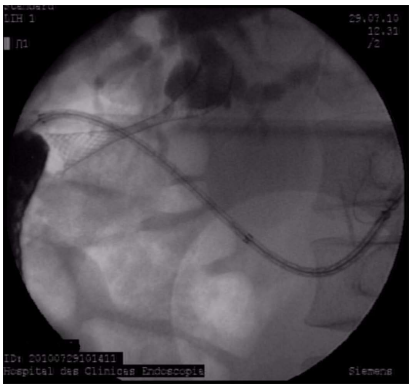

**Figure 3 Cholangiographic aspect after biliary stent release.**

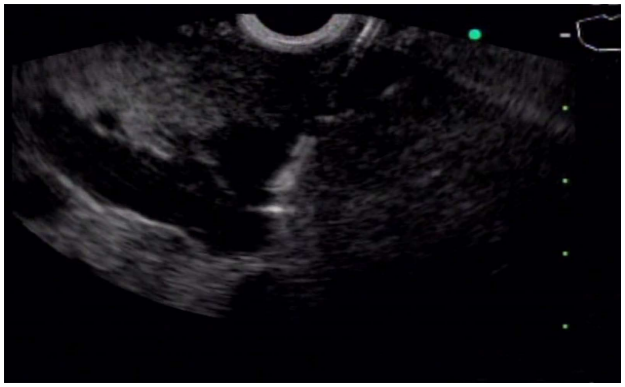

**Figure 2 Biliary puncture.**

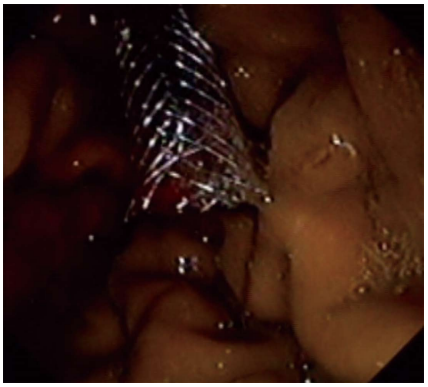

**Figure 4 Endoscopic final aspect.**

transmural access from the antral part of the stomach or duodenum[7] (Figure 2). Some endoscopists consider the latter as a route of access to the biliary system due to the anatomical position of the CBD (located in the retroperitoneal space), which might be safer in patients with ascites[18].

The stent can be inserted in the direction of the papilla (antegrade insertion, AG) or in the direction of the liver (retrograde insertion) (Figure 3). Finally, the drainage route can be transluminal {between the bile duct and either the stomach HGS or the duodenum [choledochoduodenostomy (CDS)]} or transpapillary, which, again, can be antegrade or retrograde (rendezvous, EUS-RV)[19].

The best EGBD route is not defined. Dhir *et al*[20] compare the success, complications, and duration of hospitalization for patients undergoing EUS-RV by the TH or the EH route. A total of 35 patients were analysed (17 TH, 18 EH). The mean procedure time was significantly longer for the TH group (34.4 *vs* 25.7 min; $P = 0.0004$). There was no difference in the technical success (94.1% *vs* 100%). However, the TH group had a higher incidence of post-procedure pain (44.1% *vs* 5.5%; $P = 0.017$), bile leak (11.7 *vs* 0; $P = 0.228$), and air under diaphragm (11.7 *vs* 0; $P = 0.228$). All bile leaks were small and managed conservatively. Duration of hospitalization was significantly higher for the TH group (2.52 *vs* 0.17 d; $P = 0.015$)[20]. Nevertheless, Artifon *et al*[21] compared the outcomes of 2 non-anatomic EGBD routes: Hepaticogastrostomy (HPG) - 25 patients and CD - 24 patients. HPG and CD techniques were similar in efficacy and safety (Figure 4).

Khashab *et al*[22] compared outcomes of rendezvous and transluminal techniques. During the study period, 35 patients underwent EGBD (rendezvous $n = 13$, transluminal $n = 20$). Technical success was achieved in 33 patients (94%), and clinical success was attained in 32 of 33 patients (97.0%). The mean post-procedure bilirubin level was 1.38 mg/dL in the rendezvous group and 1.33 mg/dL in the transluminal group ($P = 0.88$). Similarly, length of hospital stay was not different between groups ($P = 0.23$). There was no significant difference in adverse event rate between rendezvous and transluminal groups (15.4% *vs* 10%; $P = 0.64$). Long-term outcomes were comparable between groups, with 1 stent migration in the rendezvous group at 62 d and 1 stent occlusion in the transluminal group at 42 d after EGBD. Both rendezvous and direct transluminal techniques seem to be equally effective and safe[22].

According to previous reports, a 19G or 22G FNA needle or needle knife is used to puncture the CBD, followed by the passage of a 0.025-inch or 0.035-inch guidewire was inserted through the needle and looped in the biliary tree[7]. However, there are no randomized controlled trials comparing the outcomes of various FNA needles in the aforementioned procedure[23]. Various

devices have been previously described for dilatation of the fistula after puncturing the CBD[23]. The most common devices for transmural tract dilation are the rigid dilator 6 Fr up to 10 Fr, 4-8 mm balloon catheter, diathermic dilator or needle knife. The feasibility of graded dilation in EUS-HGS was superior to that of EUS-CDS[24].

In a series of 101 cases, Poincloux *et al*[25] placed the EUS in the cardia or the lesser curvature of the stomach and oriented it to view the dilated intrahepatic lateral sector bile ducts. Color Doppler ultrasound was used to confirm absence of vascular structures before EUS-guided puncture through the gastric body. The left bile duct puncture was performed using a 19-gauge access needle and a 0.035- inch super stiff guidewire was introduced through the EUS needle and advanced in an antegrade fashion to the main left bile duct. A hepatogastric fistula was created using a 5.5-Fr wire-guided needle-knife. 6-Fr and 7-Fr tapered biliary dilator catheters to dilate the fistula tract. Under EUS and fluoroscopic view, a stent was placed through the hepatogastrostomy between the main left bile duct and the gastric lumen.

Dhir *et al*[20] used a 19-gauge needle to puncture in the EUS-RV procedure. Attempt was made to puncture with the echoendoscope in a straight position and the needle pointing in the direction of the CBD. Once biliary access was confirmed by aspiration of 5-10 cc bile, contrast was injected to evaluate the ductal system and, a 0.032-inch hydrophilic angled-tip guide wire was inserted through the needle and directed in an anterograde fashion downstream across the stricture and/or the papilla into the duodenum. Once the guide wire crossed the papilla and looped in the duodenum, the echoendoscope was withdrawn and an ERCP scope was positioned at the papilla. Due to the short length of wire, continuous water injection was used to keep the wire in position. The guide wire was pulled into the biopsy channel of duodenoscope with a snare and ERCP was completed[20].

The stent selection is very important. Plastic stent has a low cost, but, self-expandable metal stents offer superior patency to plastic stents for palliation of malignant distal bile duct obstruction. Even though, the superiority of covered self-expandable metal stents to multiple plastic stents for treatment of benign biliary strictures has not been proven[26]. Covered metal stents may be useful to reduce bile leakage in EGBD.

## PROCEDURAL LIMITATIONS

Most studies about EGBD are single center and based on case reports or small series. Many studies described this procedure with high success rates (more than 90%) and low rate of procedure-related complications (around 19%)[27], however, data from a large multicenter retrospective trial failed to report advantages of any of these techniques[5].

The main risk of EGBD is bile leakage. Complications of all techniques combined included pneumoperitoneum in 5%, bleeding in 11%, bile leak/peritonitis in 10%, and cholangitis in 5%. Complication rates were similar in benign and malignant disease. No significant difference in complication rates was noted when comparing plastic to metal stents, although a trend toward a better outcome was observed for metal stents ($P$ = 0.09). There was a significantly higher incidence of cholangitis in patients with plastic stents (11% *vs* 3%; $P$ = 0.02)[5].

The use of a needle-knife for fistula dilation was the single risk factor for post procedural adverse events after EGBD. Thus, use of a needle-knife for fistula dilation should be avoided if possible[24], with a risk of creating an unhealthy fistula. This problem does not arise with a cystotome or ring knife fistula creation.

In Dhir *et al*[19] retrospective multicenter study, death was a major complication reported in 4% of cases. All cases used EUS-RV TH route. Nevertheless, the success rate was equal for the various techniques.

## CONCLUSION

Data involving mostly small series from expertise centers suggest that EGBD can be performed with high therapeutic success (87%) but it might be associated with 10% to 20% morbidity (mostly mild to moderate) and rare serious adverse events[28].

We recommend EGBD when bile duct access is not possible because of failed cannulation, altered upper GI tract anatomy, gastric outlet obstruction, a distorted ampulla, a *in situ* enteral stent or periampullary diverticulum, as a minimally invasive alternative to surgery or radiology.

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ORIGINAL ARTICLE

Basic Study

# Transgastric endoscopic gastrojejunostomy using holing followed by interrupted suture technique in a porcine model

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## Abstract

**AIM:** To demonstrate the feasibility and reproducibility of a pure natural orifice transluminal endoscopic surgery (NOTES) gastrojejunostomy using holing followed by interrupted suture technique using a single endoloop matched with a pair of clips in a non-survival porcine model.

**METHODS:** NOTES gastrojejunostomy was performed on three female domestic pigs as follows: Gastrostomy, selection and retrieval of a free-floating loop of the small bowel into the stomach pouch, hold and exposure of the loop in the gastric cavity using a submucosal inflation technique, execution of a gastro-jejunal mucosal-seromuscular layer approximation using holing followed by interrupted suture technique with endoloop/clips, and full-thickness incision of the loop with a Dual knife.

**RESULTS:** Pure NOTES side-to-side gastrojejunostomy was successfully performed in all three animals. No leakage was identified *via* methylene blue evaluation following surgery.

**CONCLUSION:** This novel technique for preforming a gastrointestinal anastomosis exclusively by NOTES is technically feasible and reproducible in an animal model but warrants further improvement.

**Key words:** Endoscopic gastrojejunostomy; Endoloop; Endoscopic clips; Natural orifice transluminal endoscopic surgery; Pigs



**Core tip:** A pure natural orifice transluminal endoscopic surgery gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips, without the need of any additional devices.

Chen SY, Shi H, Jiang SJ, Wang YG, Lin K, Xie ZF, Liu XJ. Transgastric endoscopic gastrojejunostomy using holing followed by interrupted suture technique in a porcine model. *World J Gastrointest Endosc* 2015; 7(15): 1186-1190 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i15/1186.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i15.1186

## INTRODUCTION

Gastro-jejunal side-to-side anastomosis is clinically designed for palliation of malignant gastric outlet obstruction (GOO)[1], performed primarily *via* open[2] and laparoscopic surgery[3]. Natural orifice transluminal endoscopic surgery (NOTES) may represent an alternative for the execution of gastro-jejunostomy procedures[4-10] due to less invasiveness and postoperative pain compared with the above-mentioned two procedures. To date, dozens of successful gastric bypass procedures by pure or hybrid NOTES have been reported, however, these methods are associated with some limitations, including being time-consuming, technically demanding and requiring specialized suturing devices.

Our experimental study aimed to demonstrate the feasibility and reproducibility of a pure NOTES gastrojejunostomy procedure using holing[11] followed by interrupted suture technique using a single endoloop matched with a pair of clips[12] in a non-survival porcine model.

## MATERIALS AND METHODS

### *Animal model*

Our study involved three healthy female domestic pigs weighing between 15 and 20 kg. All animals were fasted for 24 h prior to surgery. Induction of anesthesia was achieved *via* an intramuscular injection of 100 mg ketamine, 10 mg droperidol and 1 mg atropine, and anesthesia was maintained by intravenous drip of propofol at a rate of 10 mL/h with endotracheal intubation. Heart rate and oxygen saturation were monitored during the operation. Animals were kept in a supine position to allow for the best access and optimal peritoneal exploration. This study was approved by the Institutional Animal Use and Care Committee of Fujian Provincial Tumor Hospital, Teaching Hospital of Fujian Medical University, Fuzhou, China.

### *NOTES gastrojejunostomy*

**Gastrostomy:** A small incision was created in the horizontal portion of the anterior pre-antral zone, which was determined *via* finger indentations of the abdominal wall, away from the small and large curvature, using a Dual knife (KD650L Olympus), followed by dilation using an 18-mm CRE balloon. The dual-channel therapeutic endoscope (GIF2TQ260M, Olympus Tokyo Japan) was subsequently advanced into the peritoneal cavity through the gastrostomy site.

**Selection and retrieval of a free-floating loop of the small bowel into the stomach pouch:** Loop selection was guided by loop proximity to the gastrostomy site to minimize the risk of tension and possible ischemia. An appropriate segment of the upper small intestine on its anti-mesenteric side was grasped by an endoscopic alligator forceps (FQ-46L-1, Olympus) through one channel of the endoscope and dragged through the incision into the stomach for the intra-gastric anastomosis, taking care not to include the mesenteric vascular supply to avoid unexpected incarceration.

**Hold and exposure of the loop in the gastric cavity *via* submucosal inflation:** An endoscopic injector (NM-400L-0423 Olympus) was passed through the other channel of the endoscope. Five to ten mL mL of saline solution mixed with 0.1 mL of 2% methylene blue was immediately injected into the submucosal layer circumferentially along the periphery of the gastrostomy site. Submucosal inflation temporarily decreased the size of the orifice of the gastrostomy to prevent the loop from falling back to the peritoneal cavity.

**Execution of a gastro-jejunal mucosal-seromuscular layer approximation using holing followed by interrupted suture technique with endoloop/clips:** First, a total of five to seven holes were made circumferentially along the periphery of the gastrostomy by using the Dual knife. An endoloop followed by an endoclip delivery system was inserted into the gastric cavity through the double-channel endoscope and placed at the side of one hole. One prong of the clip

**Table 1 Summary of the procedures and outcomes following creation of pure natural orifice transluminal endoscopic surgery side-to-side gastrojejunostomy in three female pigs**

| Observation parameters | Pig 1 | Pig 2 | Pig 3 |
|---|---|---|---|
| Time required to enter the peritoneal cavity and pull the loop intro the stomach (min) | 35 | 19 | 18 |
| Time required to suture the anastomosis (min) | 58 | 44 | 47 |
| Number of the stitched pairs | 5 | 6 | 7 |
| Complications | | | |
| Minor bleeding | + | + | - |
| Anastomotic leak | - | - | - |

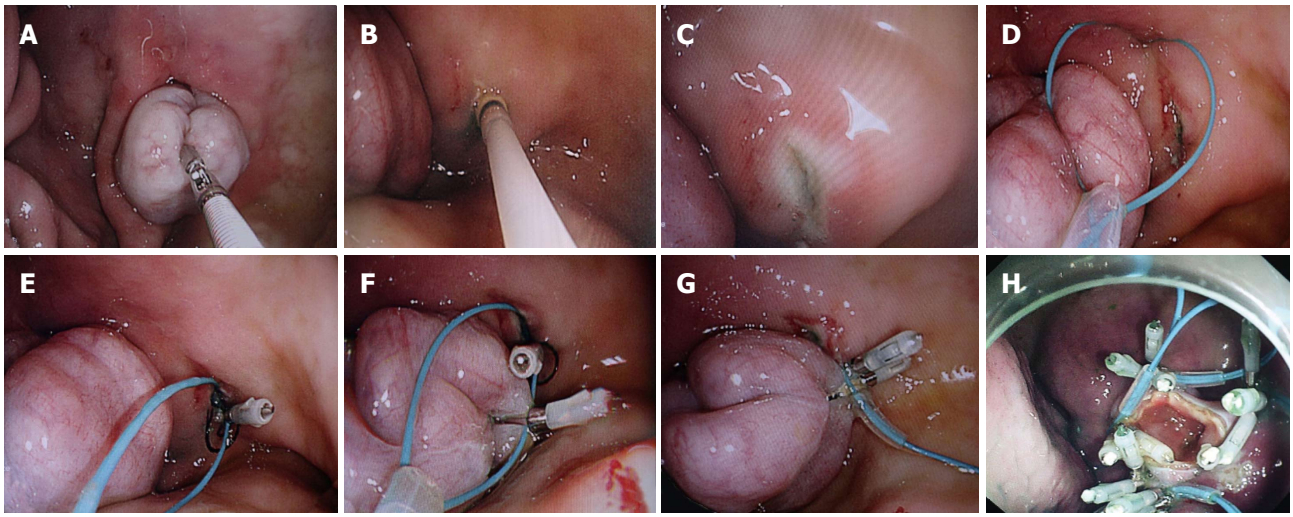


**Figure 1 Step-by-step procedure of pure natural orifice transluminal endoscopic surgery side-to-side gastrojejunostomy.** A: Endoscopic view of a loop of the small bowel in the stomach grasped by an endoscopic alligator forceps on its anti-mesenteric side; B: Image taken during submucosal injection around the loop; C: Endoscopic view of one hole made on gastric mucosal surface; D: Endoscopic view of an endoloop placed around the hole; E: Endoscopic view of one clip clipped to anchor the endoloop on the side of the stomach after the prong of the clip was inserted in the hole of the stomach wall; F: Endoscopic view of the second clip clipped to anchor the endoloop on the side of the small intestine; G: Endoscopic view of the endoloop tightened to approximate the gastric mucosal layer and the intestinal serosal layer; H: Endoscopic view of gasto-jejunal mucosal-seromuscular layer anastomosis followed by the loop full-thickness incision.

was then inserted in the hole of the stomach wall and clipped to anchor the endoloop. The second clip was used to anchor the same endoloop to the serosal surface of the small intestine. The gastric mucosal layer and the intestinal serosal layer were approximated by tightening of the endoloop. Briefly, gastro-jejunal mucosal-seromuscular layer anastomosis was created in pairs through the mucosa of the stomach and the serosa of small intestine to join the tissues based on the cooperation between one loop and a pair of clips. Five to seven pairs of interrupted sutures were placed to secure the anastomosis.

**Full-thickness incision of the loop with the Dual knife:** Jejunal loop incision was made longitudinally on its anti-mesenteric aspect to turn the inside mucosa out.

### *Euthanasia and necropsy*

Euthanasia was performed immediately after the procedure. Necropsy results including injuries to adjacent organs, vascular bleeding, anastomotic patency and leakage evaluation were recorded.

## RESULTS

Detailed data of pure NOTES side-to-side gastrojejunostomy performed on the three animals are shown in Table 1 and Figure 1. The procedure was technically successful in all cases. The duration of the procedure ranged from 1.0 to 1.5 h. Minor bleeding occurred from the right gastroepiploic artery during gastrostomy in 2 pigs and treated efficiently with the endoscopic hemostatic forceps (FD-410LR, Olympus) (80 W/soft-coagulation). On the postmortem examination, the immediate patency of the anastomosis was satisfactory, and no evidence of anastomotic leakage was identified *via* methylene blue evaluation[13] (Figure 2).

## DISCUSSION

The advent of NOTES has made a minimally invasive endoscopic technique possible for creation of gastrojejunal anastomosis, being faced with opportunities and challenges at the same time.

Previous studies[4,7,8-10] have reported three full-thickness suturing methods summarized as the small intestine being pulled into the stomach lumen and

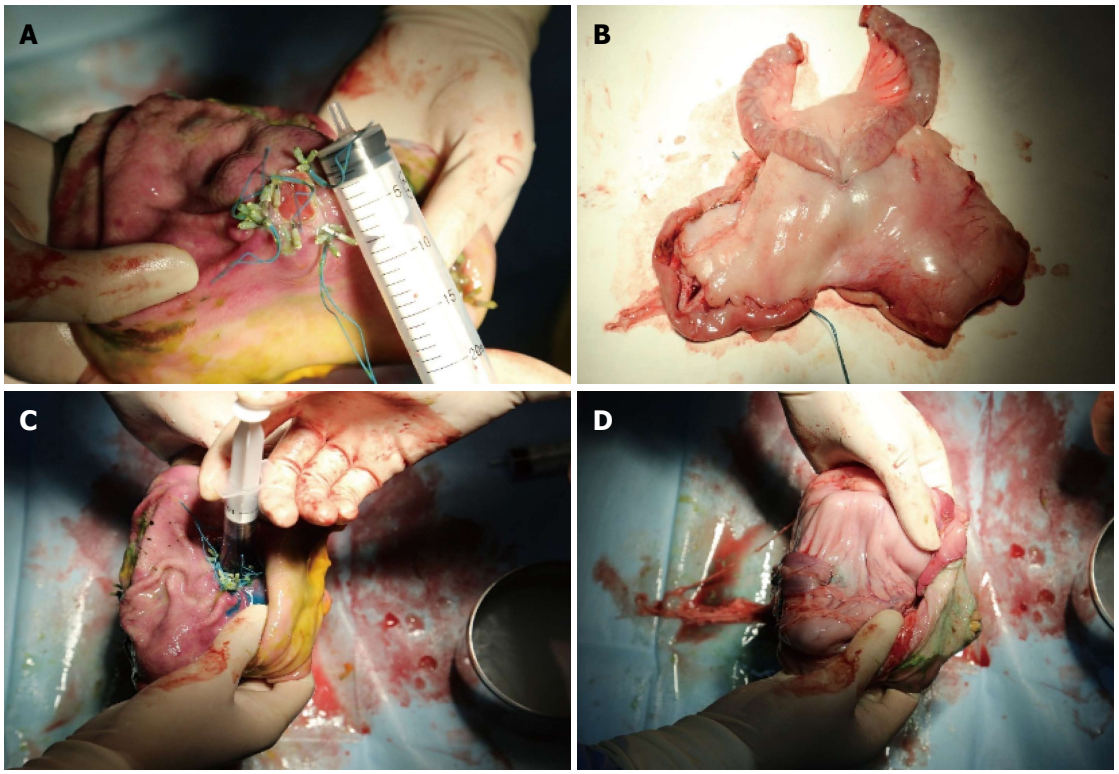


**Figure 2 Postmortem appearances of anastomosis.** A: Macroscopic appearance showing that the intestinal wall had been joined to the stomach wall; B: Macroscopic appearance of gastrointestinal side-to-side anastomosis; C: Methylene blue instilled into the anastomotic lumen; D: No methylene blue observed on the surface of gastric serosa around the anastomosis.

then sutured to the stomach wall using newly designed endoscopic suturing devices as follows: (1) a prototype endoscopic suturing device (Eagle Claw; Olympus)[7]; (2) a prototype "T-tag" suture system (BraceBar; Olympus)[4,9,10]; and (3) an EndoGIA stapler (Covidien)[8]. Here we reported for the first time, the use of interrupted suture technique using one endoloop matched with a pair of clips in a non-survival porcine model. This new technique resembles T-tag suture system, one of the aforementioned three methods, with its own unique characteristics. First, submucosal saline solution injection around the gastrostomy site made a slight cushion that prevented unexpected perforation by electric knives and allowed space to create holes deep enough to insert the prongs of the clip and to facilitate the subsequent secure clipping. Furthermore, submucosal inflation temporarily decreased the size of the orifice, and the smaller orifice allowed us to manipulate the loop of the small intestine in place more easily. Second, creating several holes at the edge of gastrostomy provided strong anchoring points for one prong of a clip in order to avoid clip slippage during grasping gastric thick mucosal surface. Third, interrupted suture method using one endoloop matched with a pair of clips was derived from the principle of "sewing" using a pair of T-tags with a single puncture needle, which may be done successfully by using only endoscopes and common endoscopic accessories, without the need of any extra devices.

In particular, if the small intestine was inadvertently dropped during the procedure, no leakage of small bowel contents occurred because the bowel wall was not incised until the anastomosis was complete.

Our pilot study had several limitations, however. First, endoscopic selection of an appropriate loop of the small bowel and secure fixation of the small bowel to the gastric wall without intra-peritoneal manipulation remains challenging[14]. In our current study, the appropriate portion of the small bowel was identified based on its proximity to the gastrostomy site and the left upper abdominal anatomical landmarks such as the spleen. For clinical studies, EUS guidance could be used to direct the targeted jejunal segment near the ligament of Treitz in non-altered anatomy patients[1,15]. Second, both of the endoscopic endoloop/clips utilized in our study, as well as the sewing devices (such as T-bar sutures) predominantly approximate the mucosa, and the reliability and durability of the anastomosis under gastric pressure should be estimated in the porcine model of GOO. Ryou *et al*[16] demonstrated that gastric mucosal closure with endoscopic clips may result in significant air and fluid leakage *via* the line of clips, however, this was not observed in our study.

In conclusion, this novel technique of performing gastrointestinal anastomosis exclusively by NOTES is technically feasible and reproducible in an animal model, although further improvement is warranted.

## COMMENTS

### Background

Gastro-jejunal side-to-side anastomosis is clinically designed for palliation of malignant gastric outlet obstruction (GOO), mostly performed *via* open and

laparoscopic surgery. Natural orifice transluminal endoscopic surgery may represent an alternative method of performing gastro-jejunostomy procedures due to its less invasiveness and lower incidence of postoperative pain compared with the above-mentioned two methods.

### Research frontiers

To date, dozens of successful gastric bypass procedures *via* either pure or hybrid natural orifice transluminal endoscopic surgery (NOTES) have been described, however, these methods are associated with some limitations, as they are time-consuming, technically demanding and require specialized suturing devices.

### Innovations and breakthroughs

A pure NOTES gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips, without the need of any additional devices.

### Applications

This study demonstrates the potential application of pure NOTES gastrojejunostomy using holing followed by interrupted suture technique using one endoloop matched with a pair of clips for palliation of malignant GOO.

### Terminology

A NOTES gastrojejunostomy using interrupted suture technique with a single endoloop matched with a pair of clips resembles the technical principle of T-tag suture system, without the need of any additional devices.

### Peer-review

The advent of NOTES has made a minimally invasive endoscopic technique possible for creation of gastrojejunal anastomosis, being faced with opportunities and challenges at the same time. A pure NOTES gastrojejunostomy procedure may be successfully performed in a non-survival porcine model using holing followed by interrupted suture technique using one endoloop matched with a pair of clips.

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ORIGINAL ARTICLE

Observational Study

# Unsedation colonoscopy can be not that painful: Evaluation of the effect of "Lamaze method of colonoscopy"

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Author contributions: The study was designed by Yu SP; data were obtained by Lin XD, Wu GY, Li SH, Wen ZQ, Cen XH, Huang XG, Huang MT; endoscopy is performed by Yu SP, Lin XD, Li SH, Wen ZQ and Cen XH; data were analyzed by Wu GY; the report was mainly written by Yu SP, Lin XD and Wu GY; all authors approved the final version.

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Conflict-of-interest statement: No conflicts of interest exist.

Data sharing statement: No additional data are available.



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## Abstract

**AIM:** To evaluate the pain relieving effect of intervention with "Lamaze method of colonoscopy" in the process of colonoscopy.

**METHODS:** Five hundred and eighty-five patients underwent colonoscopy were randomly divided into three groups, Lamaze group, anesthetic group and control group. Two hundred and twenty-four patients of Lamaze group, the "Lamaze method of colonoscopy" were practiced in the process of colonoscopy. The Lamaze method of colonoscopy is modified from the Lamaze method of childbirth, which helped patients to relieve pain through effective breathing control. One hundred and seventy-eight patients in anesthetic group accepted sedation colonoscopy. For 183 patients in control group, colonoscopy was performed without any intervention. The satisfactory of colon cleaning, intestinal lesions, intubation time, success ratio, pain grading and complications were recorded. All data were statistically analyzed.

**RESULTS:** There were no significant differences at base line of the three groups ($P > 0.05$). Anesthetic group shows advantage in intubation time than the other two groups ($P < 0.05$). Lamaze group shows no advantage

in intubation time than that in control group ($P > 0.05$). The anesthetic group showed an apparent advantage in relieving pain ($P < 0.01$). Therefore, the "Lamaze method of colonoscopy" performed in colonoscopy could relieve pain effectively comparing with control group ($P < 0.05$). The patients in anesthetic group had the highest incidence of complications ($P < 0.05$).

**CONCLUSION:** The performance of the "Lamaze method of colonoscopy" in the process of colonoscopy could relieve patients' pain, minimize the incidence of complications, and is worthy promotion in clinical practice.

**Key words:** Colonoscopy; No sedation; Pain; Lamaze technique



**Core tip:** Colonoscopy is used as primary investigation of colorectal neoplasm worldwide and is of great value in detection of colorectal cancer in early stage. Though, it is not widely accepted by patients due to the uncomfortable feeling, especially pain, during the process. Recent years, sedation colonoscopy has developed rapidly, it has led to a great promotion of the increase of the patients' acceptance of follow up examination. Therefore, complication of sedation colonoscopy such as bleeding, perforation, cardiopulmonary events happens once in a while. Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods. Here we evaluated the effect of a new method of unsedation colonoscopy we called "the Lamaze method of colonoscopy"(Lamaze colonoscopy) modified from the Lamaze method of childbirth. Our study suggested that Lamaze colonoscopy is an effective way to relief pain during colonoscopy.

Yu SP, Lin XD, Wu GY, Li SH, Wen ZQ, Cen XH, Huang XG, Huang MT. Unsedation colonoscopy can be not that painful: Evaluation of the effect of "Lamaze method of colonoscopy". *World J Gastrointest Endosc* 2015; 7(15): 1191-1196 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i15/1191.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i15.1191

## INTRODUCTION

Colonoscopy plays a big part in primary investigation of colorectal diseases and screening for colorectal neoplasm[1]. Some patients find it difficult to endure the procedure and refuse the follow up examination due to the pain during the procedure. In recent years, the administration of anesthetics during endoscopy introduced by some scholars has achieved extraordinary results[2,3]. Meanwhile, some patients are susceptible to intestinal bleeding, bowel perforation and sedation-related cardiopulmonary adverse reaction due to the loss of pain and throat reflex in anesthesia[4,5].

"The Lamaze method of childbirth", developed by the French obstetrician Ferdinand Lamaze, has been used to decrease the level of maternal pain during natural birth since late 1950s, and plays a good role in the area[6]. Pain during delivery is mainly caused by contraction of uterus. Colonoscopy requires gas infusion during the process, which can stretch the colon like a balloon if gas accumulated; the retroaction against stretching of colon may cause the pain and uncomfortable feeling[7]. The mechanism of pain in childbirth and colonoscopy is similar. We created "The Lamaze method of colonoscopy" (Lamaze colonoscopy), which was modified from "The Lamaze method of childbirth", and practiced it in the process of colonoscopy. In our study, we verified the effect of Lamaze colonoscopy in reducing pain during colonoscopy.

## MATERIALS AND METHODS

### *Patients*

The study included consecutive patients underwent colonoscopy at endoscope center in our hospital from November 2012 to October 2014. The first 3 patients whom underwent sedation colonoscopy were enrolled in anesthetic group every Monday (Monday is our sedation colonoscopy day) except for holidays and those whom needed endoscopic treatment such as polypectomy. The first 3 patients whom underwent unsedation colonoscopy were enrolled in Lamaze group every Tuesday. Those whom needed endoscopic treatment were also ruled out. The first 3 patients whom underwent unsedation colonoscopy were enrolled in control group every Thursday. Those whom needed endoscopic treatment were excluded too. Patients with severe cardiopulmonary dysfunction, stroke, moderate to severe ascites, renal insufficiency, severe malnutrition and patients who were bed ridden were excluded from the study. All patients enrolled in the experiment had signed a consent form of colonoscopy examination. Patients in anesthetic group all signed a consent form of sedation. A total of 585 patients aged from 25-82 years old were enrolled. There were 224 patients in Lamaze group, 178 patients in anesthetic group and 185 patients in control group finally.

### *Examination*

Bowel preparation was routinely accomplished with a 2 L electrolyte solution of polyethylene glycol (all patients were chinese which belongs to yellow race). All patients were given supplemental oxygen intranasal (2 L/min). Heart rate, blood pressure and oxygen saturation were monitored throughout the procedure. Intravenous sedation-analgesics provided by the anesthetist in anesthetic group using a combination of fentanyl (0.5-1 μg/kg) and propofol (1.5-2 mg/kg) at the discretion of the endoscopists. Five doctors with at least 5-years-experience of performing colonoscopy performed the procedure. We began to insert

**Table 1 Lamaze method of childbirth and the Lamaze method of colonoscopy**

| | |
|---|---|
| Lamaze method of childbirth[8,9] | Thoracic breathing: Used in initial stage of uterus contraction, method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) abdominal stay relaxed while breath in from nose, breath out from mouth; (4) a total of 6-9 times of inspiration and expiration per minute; and (5) practice 5 times a day, 60 s each time<br>Shallow and slow accelerating breathing: Use when the uterus contracts each 2-4 min, cervix opened to 2-8 cm. Method: Step (1-3) is the same with thoracic breathing; and (4) accelerate the breathing when uterus contraction enhanced, slow it down while contraction relieves<br>Shallow breathing: Use when the uterus contracts lasts for 60-90 s each 30-90 s , cervix opens to 8-10 cm Method: Step (1-2) is the same with thoracic breathing; (3) open mouth slightly to help breath (making a sound "hee-hee"); (4) breathing with nose, making noise from the larynx; (5) adjust the respiratory rate according to intensity of the contraction; (6) inspiration and expiration the same volume of air to avoid hyperventilation; and (7) 4-6 quickly continue inspiration and expiration then vigorously exhale, repeat until uterus contraction stops<br>Close air-way and force movement: Used when cervix is full opened to 10 cm. Method: (1) legs apart, hands holding handrail of obstetric delivery bed; (2) vigorously aspirated and close air-way, force down; (3) head up slightly staring at navel with jaw neck down forward; and (4) hold breath for 20-30 s as far as possible, exhale and hold breath at once and force movement until uterus contraction stops<br>Halitus movement: Used when cannot exert herself but cannot help to do it. Method: (1) mouth open, breathing quickly like gasping; and (2) the whole body is relaxed totally |
| The Lamaze method of colonoscopy | Thoracic breathing: Used when the procedure begins, method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) abdominal stay relaxed while breath in from nose, breath out from mouth; and (4) a total of 6-9 times of inspiration and expiration per minute<br>Shallow and slow accelerating breathing: Used when the scope is crossing the junction of sigmoid colon and descending colon from the sigmoid colon. Method: Step (1-3) is the same with thoracic breathing; and (4) accelerate the breathing when pain enhanced, slow it down while pain relieved<br>Shallow breathing: Used when the scope is crossing the splenic flexure. Method: (1) completely relaxed; (2) eyes fixed on a certain point; (3) open mouth slightly to help breath (making a sound "hee-hee"); (4) breathing with nose, making noise from the larynx; (5) adjust the respiratory rate according to pain intensity; (6) inspirate and expirate the same volume of air to avoid hyperventilation; and (7) 4-6 quick continue inspirate and expirate then vigorously exhale, repeat until the pain disappear<br>Close air-way and force movement: Used when the pain is moderate or severe. Method: (1) vigorously aspirated and close air-way, force down; and (2) hold breath for 20-30 s as far as possible, exhale and hold breath at once and force movement until pains relieves or disappeared |

colonoscope when patients fell asleep when their eyelash reflex disappeared, breathed calmly and muscle relaxed. Patients in Lamaze group were trained "the Lamaze method of colonoscopy" (detailed in Table 1), by the assigned nurse in endoscope center, 5-8 min before examination. It would be continuously practiced during the whole process of colonoscopy. The control group was given no intervention. The colonoscopy was categorized as completed when reached the cecum or the ileocolic anastomosis (in case of colonic surgery).

The endoscopists graded the quality of bowel preparation immediately after the procedure. Grade 1 as excellent with no stool visualized, Grade 2 as satisfactory with a small amount of stool visualized not blocking the view, Grade 3 as unsatisfactory with stool blocking the view and/or the passage of the colonoscope. He/she also evaluated the difficulty of insertion of the colonoscopy on a 100 mm visual analog scale, with 0 "very easy" and 100 "very difficult." All patients were asked to finish a questionnaire after the procedure in which they graded abdominal pain using a visual analogue scale (VAS) from 0 to 10 (0 as extremely acceptable/least severe, 10 as least acceptable/extremely severe). Patients marked the point on the line that they feel representing their pain grade. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks.

### Equipment and record

Age, gender, history of previous colonoscopy or previous abdominal surgery was recorded before examination. The satisfaction of colon cleaning, intestinal lesions, intubation time, success ratio and complications were also recorded after examination.

### Equipment and personnel

Bowel preparation was done in all patients before the examination using 2 L electrolyte solution of polyethylene glycol. Colonoscopy examinations were performed by an experienced endoscopist, using a video colonoscope (FUJINON). Technique assistance is performed by the same assistant when needed during examination. Patients were sedated in presence of an aesthetist. The endoscopists, assistant and nurse received the "Lamaze method of childbirth" course before trial. They were also trained to perform Lamaze colonoscopy using the method above.

### Statistical analysis

SPSS 19.0 was used to process data. Quantitative data were reported as means ± SD. One-way ANOVA was used to compare the age and intubation time of the three groups, least-significant difference is used to compare the differences within groups if difference is significant between groups and the test of homogeneity of variances shows $P < 0.05$. $\chi^2$ test was used to compare gender, history of previous colonoscopy, previous abdominal surgery history, intestinal lesions, success ratio and complications. The satisfactory of colon cleaning and the pain grades of the three groups were

**Table 2 Comparison on patients' age, gender, previous colonoscopy history and previous abdominal surgery history**

| | Age (yr) | Gender (male/female) | Previous colonoscopy(Y/N) | Previous abdominal surgery(Y/N) |
|---|---|---|---|---|
| Lamaze group | 54.9 ± 9.9 | 118/106 | 88/136 | 43/181 |
| Anesthetic group | 55.6 ± 9.7 | 76/102 | 62/116 | 25/153 |
| Control group | 56.3 ± 8.6 | 98/85 | 66/117 | 31/152 |
| *P* | 0.197 | 0.07 | 0.633 | 0.403 |

**Table 3 Comparison on the quality of bowel cleanliness**

| | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Lamaze group | 168 | 36 | 20 |
| Anesthetic group | 123 | 38 | 17 |
| Control group | 137 | 29 | 17 |

$\chi^2 = 2.657$; $P = 0.617$.

**Table 4 Comparison on intestinal lesions**

| | Normal | Colon polyps | Colonic diverticulum | IBD | Colon cancer |
|---|---|---|---|---|---|
| Lamaze group | 127 | 69 | 11 | 8 | 9 |
| Anesthetic group | 107 | 46 | 9 | 9 | 7 |
| Control group | 115 | 39 | 8 | 12 | 9 |

$\chi^2 = 6.293$; $P = 0.614$. IBD: Inflammatory bowel disease.

compared with crosstable Pearson $\chi^2$ test. Criterion for statistical significance was $P < 0.05$.

## RESULTS

There were no significant differences between the three groups in age, gender, history of previous colonoscopy and history of abdominal surgery (Table 2).

According the endoscopists' finding, there was no difference in the quality of colon cleanliness and the intestinal lesions between the three groups (Tables 3 and 4).

The anesthetic group was much more successful in alleviating pain comparing to the other two groups, 57.3% (102/183) of patients feel completely no pain at all. The Lamaze group of colonoscopy is also more efficient in relieving pain than the control group (Tables 5 and 6).

The time required for intubation in anesthetic group is shorter than the other two groups. But the Lamaze group did not demonstrate its improvement compared with control group in this aspect (Tables 7 and 8).

Only 1 case failed to complete colonoscopy in anesthetic group, the patient was a thin women who had a previous history of cesarean section. That number in Lamaze group and control group are 7 and 12. But there is no significant difference between the three groups ($P = 0.06$) (Table 9).

The complication rates of both the Lamaze group and control group were lower and complication is milder than the anesthetic group. In anesthetic group, 5 patients incurred a decrease of pulse oxygen saturation (< 90%), and 2 of the patients' heart rate drops to < 60 bpm, but all of them recovered immediately after effective intervention. There were no deaths in all three groups. The difference on complications of the three groups was significant ($P = 0.001$) (Table 10).

**Table 5 Comparison on patients' pain grading**

| | 0-2 | 2-4 | 4-6 | 6-8 | 8-10 |
|---|---|---|---|---|---|
| Lamaze group | 47 | 96 | 77 | 3 | 1 |
| Anesthetic group | 142 | 35 | 1 | 0 | 0 |
| Control group | 6 | 7 | 71 | 88 | 11 |

$\chi^2 = 506.579$; $P < 0.001$.

**Table 6 Further pair-wised comparison of patients' pain grading**

| | $\chi^2$ | *P* |
|---|---|---|
| Lamaze group *vs* control group | 194.43 | < 0.001 |
| Lamaze group *vs* anesthetic group | 150.92 | < 0.001 |
| Anesthetic group *vs* control group | 310.68 | < 0.001 |

**Table 7 Comparison on intubation time**

| | Intubation time (min) |
|---|---|
| Lamaze group | 9.21 ± 2.76 |
| Anesthetic group | 7.46 ± 2.93 |
| Control group | 9.45 ± 2.38 |

F = 29.696, $P < 0.001$

## DISCUSSION

Colonoscopy is used as primary investigation of colorectal neoplasm worldwide and is of great value in detection of colorectal cancer in early stage[1]. Though, it is not widely accepted by patients due to the uncomfortable feeling, especially pain, during the process. Recent years, sedation colonoscopy has developed rapidly, it has led to a great promotion of the increase of the patients' acceptance of follow up examination[10-12]. Therefore, complication of sedation colonoscopy such as bleeding, perforation, cardiopulmonary events happens once in a while[13]. Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods[14-16]. Here we evaluated the effect of a new method of unsedation colonoscopy we called "the Lamaze method

**Table 8 Further pair-wised comparisons on intubation time**

| | Mean difference | Standard error | *P* | 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| Lamaze group *vs* control group | -0.243 | 0.269 | 0.368 | -0.77 | 0.29 |
| Lamaze group *vs* anesthetic group | 1.75 | 0.271 | < 0.01 | 1.22 | 2.28 |
| Anesthetic group *vs* control group | -1.993 | 0.285 | < 0.01 | -2.55 | -1.43 |

**Table 9 Comparison on the quality of bowel cleanliness**

| | Success(Y/N) |
|---|---|
| Lamaze group | 217/7 |
| Anesthetic group | 177/1 |
| Control group | 171/12 |

$\chi^2 = 9.918$, $P = 0.06$.

**Table 10 Comparison on complications**

| | Total | Bleeding | Perforation | Cardiopulmonary complications | Normal |
|---|---|---|---|---|---|
| Lamaze group | 224 | 2 | 0 | 1 | 221 |
| Anesthetic group | 178 | 9 | 0 | 7 | 162 |
| Control group | 183 | 3 | 0 | 1 | 179 |

$\chi^2 = 18.043$; $P = 0.001$.

of colonoscopy" (Lamaze colonoscopy) modified from the Lamaze method of childbirth. The Lamaze method of childbirth could reduce pain by effective breathing and relaxation training. Acknowledge of pre-delivery and delivery rule could be applied to different stages and different grades of pain to intentionally control pain caused by contractions and other discomfort feeling. The pain was transferred since mothers focus on breathing control[17]. In our study, we found Lamaze colonoscopy which modifying from "the Lamaze method of childbirth" according to the characteristics of colonoscopy. It was applied to the examination. The results indicated that the pain could be alleviated when use Lamaze colonoscopy. The mechanism of pain during colonoscopy is similar to that of childbirth. Both are caused by the spasm of smooth muscle. But the pain during colonoscopy is artificially caused by the insertion of endoscope. Also, severe pain is caused by the knotting of endoscope during operation. Lamaze colonoscopy may could maintain a relatively constant position of intestinal tract by deepening abdominal respiration, made colonoscope passed easily.

This study compared with the difference of anesthetic group, Lamaze group and control group from several aspects at the same time. Judging from the outcome, the applications of Lamaze colonoscopy did not shorten the time of intubation. The main reason of time increasing is due to the needs of helping patients get into the right step during operation. Considering from the success ratio, the anesthetic group got the highest success ratio, but it did not demonstrate a statistical difference. Too many factors working on the success ratio, research shows that age, gender, preparation of intestine, history of previous abdominal surgery, chronic colitis all contribute to it[18,19]. There is no statistical difference among the three groups in age, gender, preparation of intestine, history of previous abdominal surgery and intestinal lesions.

The usage of sedatives in colonoscopy obviously improves the acceptance and tolerance of the examination in patients. However, some issues still cannot be avoided in anesthetic colonoscopy. Venous channel must be built before the exam, medical fee increased, recovery time was prolonged, complications such as cardiopulmonary events happens. The usage of sedatives can suppress respiratory directly, causing blood pressure drops. Severe allergic reaction can be life threatening, anesthetic colonoscopy causing aspiration pneumonia leads to Acute Respiratory Distress Syndrome (ARDS) finally caused death is reported in China[20]. In this study, 2 subjects' heart rate decrease to < 60 beat per minute, 5 subjects' $SPO_2$ declined to less than 90% in anesthetic group, all those recovered after proper intervention. The incidence rate of complication especially severe complication is lower in Lamaze group and control group than that in anesthetic group. There is some deficiency in our study, the follow-up period is only one week, some delayed complication might be neglected. Some studies expended the follow-up period up to 30 d in accordance with complication[5,21]. This is a single center study, multiple center study using the same standard may provide more evidences of the value of Lamaze colonoscopy.

To sum up, the application of "the Lamaze method of colonoscopy" in colonoscopy can ease the pain of patient effectively, enhance the tolerance of colonoscopy and avoid the adverse effect of anesthetics. This method is worthy of wide promotion, summary and improvement.

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## COMMENTS

### Background

Colonoscopy plays a big part in primary investigation of colorectal diseases and screening for colorectal neoplasm. Some patients find it difficult to endure the procedure and refuse the follow up examination due to the pain during the procedure. Sedation colonoscopy developed quickly in recent years, but the adverse reaction happens once in a while. Some unsedation colonoscopy had been used to relieve patients' pain.

### Research frontiers

Some kinds of unsedation colonoscopy had been reported by several scholars. Music, warm water infusion is the two most often reported methods. They can all relief pain during unsedation colonoscopy, but not as effect as sedative colonoscopy. New method could be explored.

### Innovations and breakthroughs

The use of Lamaze colonoscopy modified from Lamaze childbirth had never been reported. They explored the possibility of it, which is another way of pain-relief in patient undergoes colonoscopy.

### Applications

The application of "the Lamaze method of colonoscopy" in colonoscopy can ease the pain of patient effectively, enhance the tolerance of colonoscopy.

### Peer-review

The study is interesting and can be very useful in the pain-relief area of study.

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