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The diagnostic and therapeutic utility of endoscopic ultrasound in pancreatic and bile duct disorders

Ph.D. thesis

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LIST OF ABBREVIATIONS

AGA – American Gastroenterological Association

ALP – alkaline phosphatase

ANC – acute necrotic collection

APFC – acute pancreatic fluid collection

ASGE – American Society of Gastrointestinal Endoscopy

BD-IPMN – branch duct intraductal papillary mucinous neoplasm

CBD – common bile duct

CE-EUS – contrast enhanced endoscopic ultrasound

CI – confidence interval

CT – computer tomography

DEN – direct endoscopic necrosectomy

DPPS – double pigtail plastic stent

ERCP – endoscopic retrograde cholangiopancreatography

ESGE – European Society of Gastrointestinal Endoscopy

EUS – endoscopic ultrasound

FNA – fine-needle aspiration

FNB – fine-needle biopsy

GGT – γ -glutamyl transferase

GOT – glutamate-oxaloacetate transaminase

GPT – glutamate-pyruvate transaminase

IAP – International Association of Pancreatology

IOC – intraoperative cholangiography

IPMN – intraductal papillary mucinous neoplasm

LAMS – lumen-apposing metal stent

MCN – mucinous cystic neoplasm

MD-IPMN – main duct intraductal papillary mucinous neoplasm

MRCP – magnetic resonance cholangiopancreatography

MRI – magnetic resonance imaging

PCN – pancreatic cystic neoplasm

PDAC – pancreatic ductal adenocarcinoma

PFC – pancreatic fluid collection

PPS – prophylactic pancreatic stent

SCN – serous cystic neoplasm

SD – standard deviation

seBI – serum bilirubin

US – transabdominal ultrasound

WON – walled-off pancreatic necrosis

1. INTRODUCTION

1.1. General

Pancreatobiliary diseases constitute a broad, heterogenous complex group of both benign and malignant conditions. The accurate diagnosis of several pancreatobiliary diseases is clinically challenging, resulting in a significant burden on current healthcare resources. The management and treatment of pancreatobiliary disorders can be associated with significant morbidity and mortality due to the complexity of these diseases. These complex issues have supported the development of advancements, leading to a greater understanding of the pathophysiological basis and clinical manifestations of these conditions, which contributed significantly to the progress in diagnosis and treatments in the recent years. [1]

Digestive endoscopy has been recognized for long as an essential complement to internal medicine gastroenterology and gastrointestinal surgery, although it has evolved into an independent subdiscipline. Beyond its conventional diagnostic and screening applications, endoscopic procedures now play a crucial role in the treatment and palliation of different gastrointestinal disorders. [2]

Endoscopy was traditionally considered primarily as a diagnostic modality. However, in recent decades, there has been a remarkable expansion of the operative potential with certain techniques evolving into predominantly interventional endoscopic methodologies. Apart from diagnostic, screening and follow-up procedures, interventions such as complete removal of precancerous lesions in the gastrointestinal tract (e.g. polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection), as well as palliation of surgically irresecable lesions (e.g. endoscopic dilation, self-expandable metallic stent insertion) has become more available and applied techniques worldwide. [2]

This shift in paradigm has not only influenced the perspective of endoscopist but also reshaped the mindset of allied specialties. Currently, there is a growing need and expectation for specialized centers which perform more and more invasive endoscopic procedure that require a higher level of professional expertise, however carrying greater procedural risks, while offering patients a considerably reduced burden compared to traditional surgical approaches. [2]

The endoscopic retrograde cholangiopancreatography (ERCP), which is nowadays primarily utilized for therapeutic purposes, allows a range of various interventions including the extraction of bile duct stones, cytological sampling of the bile and pancreatic ducts, achievement of the adequate flow of bile and pancreatic juice by inserting stents, and dilatation of benign and malignant strictures. [2]

Endoscopic ultrasound (EUS) is considered as the gold-standard diagnostic modality for the evaluation and local staging of bilio-pancreatic disorders. Its exceptional importance lies in its ability to provide high-resolution and structural visualization as well as facilitates precise targeted tissue sampling using fine-needle aspiration (FNA) or even fine-needle biopsy (FNB) techniques. EUS-guided transluminal interventions as an advanced and minimally invasive therapeutic procedures (e.g. drainage of pancreatic fluid collections [PFCs] and necrosis, biliary drainage, celiac plexus blockade and neurolysis, tumor ablation) offer the integration of endoscopic visualization with ultrasound and fluoroscopic imaging modalities, often referred as a comprehensive trimodal imaging method. [2]

1.2. Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

1.2.1. Background

Gallstone disease is one of the most common gastrointestinal disorders requiring surgical and endoscopic interventions. [3] The incidence of gallstone disease in Western countries ranges from 5% to 22%, with approximately 8% to 20% of cases attributed to choledocholithiasis. [3] However, cholelithiasis frequently remains clinically silent, making it challenging to accurately estimate the true prevalence of gallstone disease within the general population. [3, 4] Approximately only one-third of gallstone cases present with symptomatic manifestations. [4, 5, 6] The leading etiology of obstructive jaundice is biliary calculi, accounting for 54% of cases, followed by Vater's papilla tumor (17%), pancreatic head tumor (13%), common bile duct (CBD) stricture (5%), cholangiocarcinoma (2%), and Klatskin tumor (2%) in prevalence. Approximately 7% of cases with obstructive jaundice have unknown etiology. [4, 7] Due to its frequent occurrence, gallstone-related disease is one of the most common gastrointestinal

conditions resulting in acute hospitalizations. [4, 5, 6] Accurate preoperative identification of choledocholithiasis is essential for patients indicated for cholecystectomy to minimize the surgical risks and reduce healthcare expenses. [4, 8] Various diagnostic modalities can be utilized for the confirmation of choledocholithiasis, encompassing clinical symptomatology, laboratory parameters and imaging. [4] Intraoperative cholangiography (IOC) during cholecystectomy also serves as a valuable tool in the diagnostic process of choledocholithiasis. [4]

Choledocholithiasis can easily lead to biliary obstruction, consequently causing jaundice and potentially serious complications such as acute cholangitis or acute biliary pancreatitis. If the clinical presentation progresses, life-threatening conditions can arise, making prompt interventions essential. [3]

1.2.2. Imaging methods for the diagnosis of choledocholithiasis

The diagnostic applications of imaging modalities are crucial in the assessment of choledocholithiasis. The modalities should possess the potential to detect even small stones within the bile duct. [4]

While transabdominal ultrasound (US) is being highly sensitive for diagnosing cholelithiasis, its effectiveness in identifying choledocholithiasis is compromised. [4] The sensitivity of US for detecting bile duct stones is relatively modest, ranging from 22% to 55%. [9, 10, 11] US shows higher sensitivity in identifying bile duct dilation caused by the presence of stones. [9, 10] Given the relatively low prevalence (5%-10%) of choledocholithiasis among patients with symptomatic cholelithiasis, a normal bile duct US demonstrates a negative predictive value of 95% to 96%. [10, 12, 13]

Computer tomography (CT) demonstrates superior sensitivity to US in diagnosing choledocholithiasis; however, its employment as the primary diagnostic tool is limited by concerns regarding radiation exposure and costs. [4] Non-surgical imaging modalities, including magnetic resonance cholangiopancreatography (MRCP), EUS and ERCP provide accurate visualization of choledocholithiasis with comparable sensitivities. [4]

Choledocholithiasis is accompanied by CBD dilation in majority of cases. [4] MRCP is commonly used as a non-invasive imaging modality to assess choledocholithiasis, particularly in cases associated with CBD dilation. [4] MRCP is even showing similar diagnostic accuracy to ERCP, on the other hand, MRCP is generally

restricted to patients with clear indications due to its inherent limitations. CBD dilatation has many etiologies. [4] In cases of CBD dilation diagnosed by MRCP, further ERCP examination is often necessary to provide accurate diagnosis and clarify the etiology of the dilation. [4] However, the unnecessary utilization of ERCP can be associated with significant complications. [4] Despite the advancement in MRCP techniques for imaging biliary diseases, its clinical use is limited by the need for contrast agents and the inability to provide histological diagnoses. In contrast, EUS has emerged as a valuable tool for the evaluation of biliary disorders. [4] EUS offers the opportunity for histopathological examination through biopsy sampling and facilitates the assessment of invasion and local staging of malignant lesions. [4] Moreover, EUS is considered a superior diagnostic modality for the evaluation of unexplained CBD dilation when MRCP fails to provide conclusive evidence. [4] The increasing availability of EUS in healthcare facilities, along with its superior diagnostic accuracy compared to MRCP, suggests that EUS should be considered an integral part of the management of choledocholithiasis. [4, 6, 8]

1.2.3. Laboratory assessment

The assessment of serum liver laboratory tests might be the first diagnostic step in the diagnosis of choledocholithiasis. They possess a great utility in the exclusion of CBD stones. [10] The negative predictive value of complete laboratory normal serum liver enzymes exceeds 97%. In contrast, the positive predictive value of an abnormal serum liver enzymes is 15%. [12] Although certain studies have reported marginally improved positive predictive values for CBD stones with abnormal serum bilirubin (seBi), alkaline phosphatase (ALP), or γ-glutamyl transpeptidase (GGT) levels, these values generally range from 25% to 50%. [12, 14, 15, 16] These obstructive serum liver biochemical tests tend to progressively increase with the duration and severity of the biliary obstruction, thereby augmenting the likelihood of CBD stones by 60% [14, 15], while the specificity rose to approximately 75% at a cutoff of 4 mg/dL. [14] Nonetheless, patient series with choledocholithiasis have reported mean bilirubin levels ranging from 1.5 to 1.9 mg/dL, [15, 16] and only a minority (one-third or less) of patients with choledocholithiasis present with a bilirubin level of 4 mg/dL or higher. [14, 15]

1.2.4 The role of endoscopic retrograde cholangiopancreatography in the management of choledocholithiasis

ERCP is regarded as the gold standard diagnostic and therapeutic tool for choledocholithiasis. However, being an invasive endoscopic procedure, ERCP can be associated with potential iatrogenic complications of significant severity. Therefore, its indication should be based on well-established clinical factors. Inappropriate utilization of ERCP examinations may result in an elevated rate of complications and, not least, importantly, increased healthcare costs. [4, 9, 10, 17, 18, 19, 20, 21]

ERCP carries a spectrum of potential complications, including pancreatitis (1.3%-6.7%), infection (0.6%-5.0%), hemorrhage (0.3%-2.0%), and perforation (0.1%-1.1%). [10, 18] Distinct patient characteristics such as young age and female gender have been identified as predisposing factors for pancreatitis. Coagulopathy amplifies the risk of bleeding, and immunosuppression augments the vulnerability for infection after ERCP. [10, 20] Given the elevated risk of encountering adverse events associated with ERCP in contrast to non-invasive biliary imaging methodologies or EUS, the utilization of ERCP as a diagnostic approach is optimally indicated for patients characterized by a high likelihood of choledocholithiasis, due to their increased likelihood of gaining substantial therapeutic benefits from the therapeutic capacity offered by ERCP. Studies where biliary sphincterotomy and duct sweeping with balloons/baskets were used, the sensitivity of ERCP with cholangiography has been documented to fall within the range of 89% to 93%, with a specificity of 100% for choledocholithiasis. [10, 17, 22]

Instances of false-negative outcomes in ERCP concerning choledocholithiasis are commonly seen in scenarios characterized by the presence of small stones within a dilated duct. [10] Therefore, the assessment of risks should be tailored to the specific circumstances of each individual patient. [10]

1.2.5 Recommendations based on current guidelines

The diagnosis of choledocholithiasis and the indication for ERCP are established based on the clinical manifestations, cholestatic laboratory profile, and imaging findings. [9,10] In cases of suspected choledocholithiasis, the analysis of serum liver function parameters (obstructive enzymes) and US are crucial. [9,10] Although no single variable is sufficient enough to predict adequately the presence of choledocholithiasis in

symptomatic or asymptomatic patients. The likelihood of choledochal stones is higher when multiple concurrent abnormal prognostic indicators are present. [14, 23, 24]

Numerous prognostic scoring systems and algorithms have been developed to assess the likelihood of bile duct stones. [14, 15, 23] While no single scoring system is universally accepted [10]; the most widely utilized is perhaps the 2010 recommendation issued by the American Society for Gastrointestinal Endoscopy (ASGE) (Table 1.) and its modified version in 2019 (Table 3., see METHODS). These position statements categorize patients into low, intermediate, and high probability groups for choledocholithiasis based on the patient's age, liver function laboratory values, and specific abnormalities observed on US. The diagnostic accuracy of the ASGE recommendations has been evaluated in multiple studies, revealing relatively poor diagnostic scores (sensitivity: 47,4%, specificity: 73%). [25, 26] In certain cases, ERCP is performed even when choledocholithiasis is not ultimately confirmed (in approximately one-third of cases). [9, 27, 28]

The EUS diagnostic accuracy has been demonstrated in various indications through numerous studies. In the hands of expert examiner, it is considered the most sensitive imaging modality for pancreatic and biliary diseases. Therefore, EUS has exceptional potential capability in the detection of choledocholithiasis without the risk of complications associated with ERCP. [9, 28, 29, 30]

Table 1. *Predictors and likelihood groups of choledocholithiasis based on the ASGE guideline from 2010* [10]

ASGE, 2010	
Predictors of choledocholithiasis	
Very strong	
CBD stone on transabdominal US	
Clinical ascending cholangitis	
Bilirubin >4mg/dl (>68.4 μmol/l)	
Strong	
Dilated CBD on US (>6mm with gallbladder in situ)	
Bilirubin level 1.8-4mg/dl (30.8-68.4 μmol/l)	
Moderate	
Abnormal liver biochemical test other than bilirubin	
Age older than 55 years	
Clinical gallstone pancreatitis	
Assigning a likelihood of choledocholithiasis based on clinical	
Presence of any very strong predictor	High
Presence of both strong predictors	High
No predictors present	Low
All other patients	Intermediate

1.3. Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

1.3.1 Prevalence of PCNs

Pancreatic cystic neoplasms (PCNs) affect a large percent of the general population. The prevalence varies across different studies [31, 32], according to epidemiological investigations, they can be present in 2–45% of the general population [31, 33], and this prevalence ramps up with advancing age, reaching up to 10% in individuals aged 70 years or older. [34, 35] The prevalence of incidental pancreatic cysts has been observed to be substantial in autopsy series, reaching approximately 24%. [31, 36]

Cystic lesions of the pancreas were believed to be exceedingly uncommon (it was believed that many cystic lesions were pseudocysts and neoplasms constituted less than 10%) [35], but nowadays PCNs are known to be common pathological entities, more and more frequently encountered as incidental findings in the clinical practice. [31, 37] As a result, physicians encounter the complex challenges associated with both diagnostic and therapeutic decisions. Pancreatic cysts constitute a heterogeneous spectrum of entities, including congenital, inflammatory, and neoplastic lesions. The former categories include benign characteristics and generally do not require further medical intervention unless presenting with symptoms. In contrast, some neoplastic cysts carry malignant potential or may even manifest as malignancies. [31, 34] Given the potential malignancy associated with some neoplastic entities, it is crucial to identify them at early stage and consider possible therapeutic measures. [31, 38]

The diagnosis of pancreatic cysts is progressively becoming more prevalent due to the heightened awareness of their existence and the extensive utilization of advanced, high resolution cross-sectional imaging modalities (CT, magnetic resonance imaging [MRI]). [31, 32, 34, 35, 38, 39, 40, 41] Prior investigations concerning the prevalence of PCNs were carried out utilizing US, CT, and MRI, each having distinct sensitivities for cyst identification. [31, 38, 40] The prevalence of incidentally identified cysts varies between 0.2% and 2.6% with the use of US or CT and can reach up to 19.6% when employing an MRI. MRCP is recognized with the highest sensitivity in the assessment of fluid-filled structures within the pancreatic context, encompassing both the ductal system

and cystic formations. The notable prevalence of 59.5% can be rationalized by the inherent superiority of MRCP in providing enhanced contrast for smaller cysts, facilitated by its high sensitivity to fluid content in these structures. [31, 36]

1.3.2 Clinically fundamental PCNs

1.3.2.1 General

Pseudocysts, serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) constitute the primary spectrum of cystic lesions in the pancreas. Pseudocysts, making up approximately 70% of all pancreatic cysts. [39, 42] Asymptomatic cysts can represent benign, premalignant, or malignant conditions meanwhile elevated malignancy rates are mainly linked to symptomatic cysts. Less than 1% of cases are primary pancreatic cystic cancers, whereas between 10% and 15% of cases are neoplastic cysts. [39, 43] MCNs tend to manifest in middle-aged women. SCNs are commonly identified in older women. [39, 44] These cystic pancreatic neoplasms are often referred to as representing a "mother" and “grandmother" lesions. SCNs can manifest also in males, their occurrence is more prevalent among females. [39, 45]

1.3.2.2 Mucinous cystic neoplasms

MCN is a relatively rare, usually solitaire, representing around 25% of the surgically resected cystic lesions. [46, 47, 48, 49, 50] MCNs are characterized by the production of mucin and feature an ovarian-type stroma. [39, 46] A substantial majority (95%), of MCNs are identified in females, whereas the incidence in males is lower (2% to 5%). The median age at diagnosis for both MCN and IPMN is around 45 and 48 years (16-84 years). [46, 48, 49] MCNs are predominantly localized in the body of the pancreas or the distal pancreas region (>95%) [39, 46, 47, 48, 49, 50] They encompass a spectrum including MCNs, borderline cases of MCN, as well as non-invasive and invasive forms of mucinous cystadenocarcinomas. [39]

MCN’s diameter can reach even up to 35 cm in diameter. The cyst usually has fibrous pseudocapsule with varying thickness and calcifications can be also observed. Generally presenting as unilocular, but multilocular morphology is also common. The intracystic mural nodules correlate with malignancy [48, 51, 52]

The diagnosis mostly incidental, approximately 10% manifest with acute pancreatitis, and an additional 12% exhibits palpable mass. [46, 48, 49] The incidence of malignancy in MCNs is around 17.5%. In a specific surgical series, all instances of malignant tumors were characterized by the presence of nodules or with an overall diameter exceeding 4 cm. [48, 49] This observation suggests that malignant MCNs tend to be significantly larger (with an average size of 8.2 cm as opposed to 4.5 cm) and are typically diagnosed in older patients (with an average age of 49.5 years compared to 44 years). However, the relatively rare prevalence of adenocarcinoma within MCNs indicates that not all cases undergo malignant transformation. [48]

1.3.2.3 Serous cystic neoplasms

SCN represents a benign, indolently proliferating neoplasm, and approximately 75% of cases are female. The mean age of patients undergoing surgical resection is 62 years. [41, 48, 53, 54, 55] SCNs are relatively rare neoplasms, comprising approximately 1% to 2% of all exocrine pancreatic tumors. [39, 56] Within the spectrum of surgically excised cystic pancreatic tumors, SCNs contribute to approximately 16% of cases. [53, 55]

The typical SCN usually consist of numerous small cysts, surrounded by a glycogen-rich cuboidal epithelium, imitating the characteristic "honeycomb" configuration. An alternative morphology variant characterized by oligocystic or macrocystic features is observed in roughly 10% of instances. [48, 55] SCNs can manifest in any anatomical region of the pancreas. [48] Once SCN reaches a size of around 4 cm, their growth rate may escalate significantly (up to 2 cm per year). [39, 57]

SCN with greater dimension and localized in the pancreatic head can be suspicible for malignancy. [48, 58] Malignant SCNs account for less than 1% of cases. [41, 48, 53, 54,] The diagnosis mostly depends on the classical radiological morphology characterized by the "spongy" multilocular mass, frequently exhibiting central calcification. However, it is important to note that central calcification is only observable in approximately 30% of cases. [48, 59] Most patients presenting with SCNs usually remain asymptomatic, and their clinical course primarily entails conservative monitoring and periodic imaging assessments, obviating the necessity for surgical intervention. [41, 54, 60]

1.3.2.4 Intraductal papillary mucinous neoplasms

IPMNs are characterized by their capacity to produce mucin and originate from the pancreatic ductal epithelium. It presents a spectrum of manifestations, including the branch, main duct, and the mixed (or combined) type. IPMNs can be further classified into benign, borderline, and non-invasive or invasive mucinous adenocarcinomas. Clinical presentations of IPMNs may encompass symptoms like abdominal pain and episodes of pancreatitis, alongside the potential for incidental detection. Notably, the distinguishing ovarian-type stroma, characteristic of MCNs, is not observed in IPMNs. [39]

Although the occurrence of carcinomatous invasion is reported to range from 30% to 50% in main duct IPMNs (MD-IPMNs) or mixed-IPMNs, the sensitivity of preoperative imaging modalities remains suboptimal, with the detection of invasive cancers preoperatively falling short of 80%. [48] The branch duct IPMN (BD-IPMN) may show diagnostic challenges, often being misdiagnosed as MCNs, despite the entities in terms of their epidemiology and associated cancer risk is different. [48, 61] The cumulative risk of carcinomatous transition in BD-IPMNs is approximately at 24% within surgically resected series, whereas surveillance studies estimate an annualized incidence of malignancy transformation ranging between 1% and 2%. [35, 48, 62]

IPMNs have witnessed a marked upsurge, with a notable escalation in the number of individuals undergoing surgical resection due to this condition. This trend now accounts for up to 50% of all surgically managed pancreatic cysts, signifying a substantial contrast compared to the mere 3% prevalence prior to 1990. [47, 48] Propelled by the augmented utilization of cross-sectional imaging in both pancreatic and non-pancreatic diagnostic contexts, the predominant presentation of IPMNs has undergone transformation over the years. Notably, a significant proportion of IPMNs, particularly those of the BD-IPMNs, are encountered incidentally. Overall, symptomatic manifestations are observed in a range spanning from 2% to 20% of affected individuals, with common symptoms including abdominal pain, pancreatitis, and jaundice. [47, 48]

Surgically resected non-invasive IPMNs confer a 5-year survival rate within the range of 90% to 100%. In contrast, surgically managed invasive IPMNs exhibit 5-year survival rates ranging from 31% to 60%. [48, 63]

1.3.2.5 Main duct and mixed type IPMN

Main and combined type IPMNs (Figure 1.) exhibit a predominant male predominance globally. [48, 64] The median age at the time of diagnosis is 66 years (31-87 years). [48, 61] Among the presenting clinical features, abdominal pain emerges as the most prevalent, accounting for 55% of cases, followed by weight loss (45%), jaundice (17%), and episodes of acute pancreatitis (15%). Around 17% of cases are ascertained incidentally. [48, 61] It is usually localized within the proximal pancreas in two-thirds of cases, primarily involving the pancreatic head, while a more diffuse distribution involving the entire gland is observed in 8% of instances. A protuberant Vater papilla expelling mucus can be visualized by endoscopy, which called “fish-eye sign”. This phenomenon, observed in approximately one-third of MD-IPMNs. This feature tends to be more consistently apparent in advanced disease stages, occurring in 73% of cases manifesting carcinoma in situ or invasive cancer, while being noted in 39% of instances characterized by hyperplasia and adenoma. [48, 65]

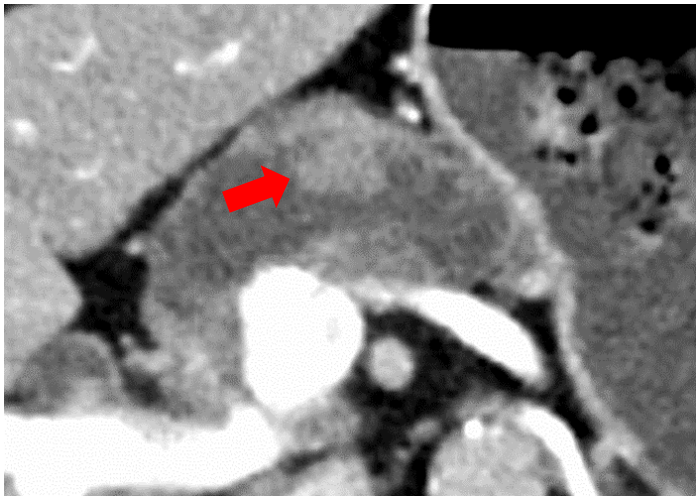

Figure 1. *Axial reconstructions of the portal venous phase CT scan of a main duct type intraductal papillary mucinous neoplasm (MD-IPMN). The arrow indicates tumor tissue proliferation originating from the wall of the main pancreatic duct associated with extreme ductal dilatation. (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.3.2.6 Branch duct intraductal papillary mucinous neoplasm

BD-IPMNs (Figure 2.) account for a substantial proportion of the progressively identified asymptomatic incidental pancreatic cysts. [32, 48]. Enhanced imaging techniques and refined pathologic evaluation have enabled the recognition of BD-IPMNs as not solely isolated anomalies, but rather as a diffuse and multifocal lesion. This broader perspective reveals that between 21% to 41% of affected individuals exhibit multiple BD-IPMNs, and varying in dimensions, distributed across their pancreatic parenchyma. [35, 48] This concept of a "field defect" carries implications not only for diagnostic considerations but also for the realm of postoperative surveillance. The follow-up over the residual pancreas following the resection of a non-invasive BD-IPMN is critical due to the potential for the progression of residual BD-IPMNs and the emergence of new BD-IPMNs, often co-occurring with pancreatic ductal adenocarcinoma (PDAC). [35, 48]

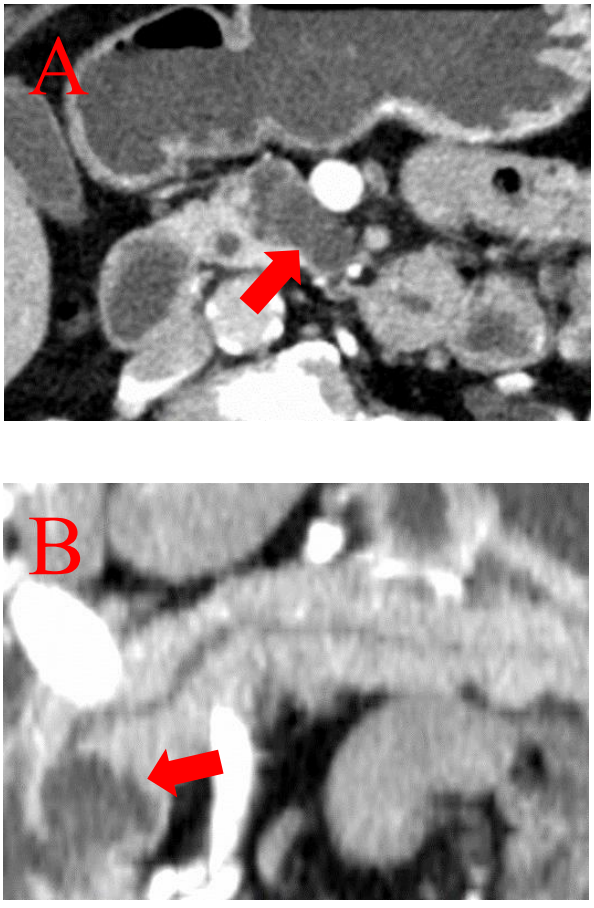

Figure 2. *Axial (A) and curved planar (B) reconstructions of the portal venous phase series of a branch duct type intraductal papillary mucinous neoplasm (BD-IPMN). (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.3.3 The role of US, CT MRI and EUS in the diagnostic process

Imaging plays a crucial role in the evaluation of all types of pancreatic neoplasms. [39] Cross sectional diagnostic methods serve a significant part in screening the cystic neoplasms, describing their anatomical details, identifying additional lesions, and characterizing invasive attributes as they grow larger. [39] The current diagnostic accuracy of cross-sectional imaging modalities for PCNs ranges from 47% to 78%. [31, 37, 66, 67]

1.3.3.1 Pseudocyst

Pseudocysts often manifest as unilocular formations exhibiting well-defined anechoic or hypoechoic (hemorrhagic or proteinaceous structure) attributes on the US. [39] Limitations of US include the retroperitoneal locations, potentially shadowing by adjacent bowel gas, and due to operator-related factors. [39] On CT scan they are usually represented by low-attenuation characteristics while MRI can often show heightened signal intensity on both T1-weighted and T2-weighted sequences, due to the hemorrhagic or proteinaceous materials within the cystic cavities. [39] The potential communication with the pancreatic duct usually can be visualized on CT or MRI. The interior of the cyst does not enhance, but the wall does on cross sectional imaging [39] Generally, mural nodules are not a characteristic feature. Although their walls might initially present irregularities, these tend to smoothen and become well-defined over time. Typically, their walls are thin, but thickened walls can be also represented. [39, 68] It is worth noting that pseudocysts can exhibit locally aggressive behavior, leading to erosion of neighboring blood vessels and the development of pseudoaneurysms. [39, 69]

1.3.3.2 Mucinous cystic neoplasm

MCNs generally exhibit a cystic morphology with fewer than 6 lobes, but the cystic segments can exceed 2 cm in dimension. These structures may display hyperechoic features due to the presence of mucinous content. [39] Peripheral calcifications may be observed in approximately 15% of cases, but not exhibiting clear visibility on MRI [39, 70, 71, 72] MCNs typically manifest elevated T2 signal intensity and varying T1 signal intensity (based on the protein content of the cyst) and wall enhancement can be also observed. Intracystic nodules and asymmetrically thickened walls could mean the present of malignancy. [39, 70, 71, 72] (Figure 3.)

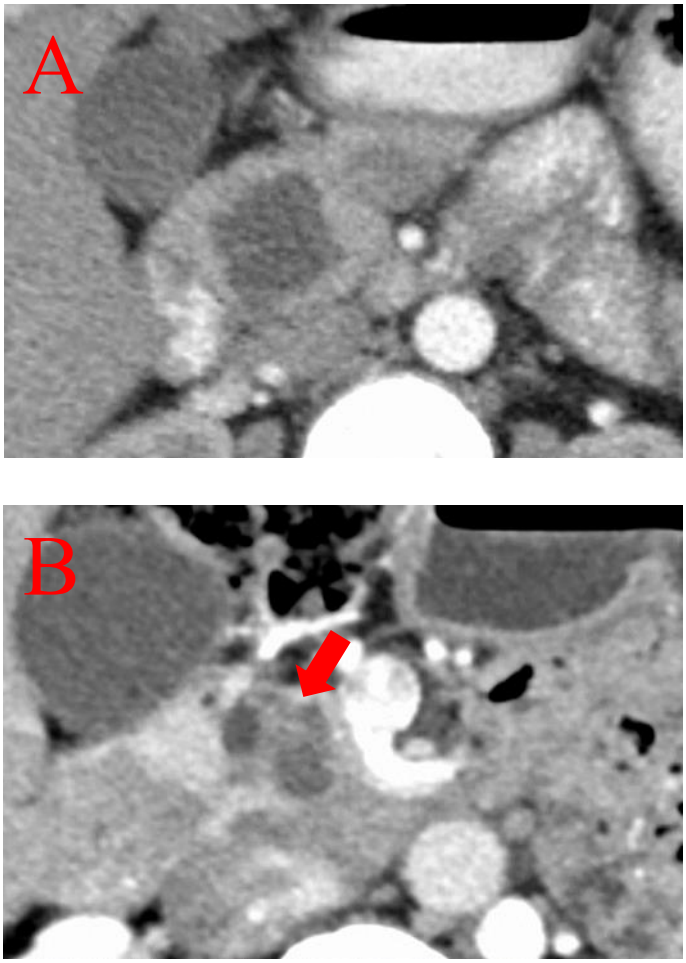

Figure 3. *The malignant transformation of a mucinous cystic neoplasm (MCN) of a 52-year-old female: axial reconstruction of the portal venous phase series of the first (A) follow-up CT scan that showed an unilocular cystic tumor in the head of the pancreas characteristic for MCN without worrisome features. The second (B) follow-up CT examination revealed the appearance enhancing thickened internal septa (arrow) considered as worrisome feature, sign of malignant transformation. (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.3.3.3 Serous cystic neoplasm

SCNs are usually characterized by more than 6 lobules, along with cystic components smaller than 2 cm. The US appearance of SCNs is mostly hyperechoic due to the presence of septations and the relatively small size of the cysts. In instances where the cysts are at a larger size, they can be visualized as anechoic elements contained within a primarily hyperechoic solid mass. The presence of calcifications manifests as hyperechoic structures with posterior shadowing. [39] On CT, due to the hypervascularization of septa, during the pancreatic parenchymal phase, they may exhibit pronounced enhancement, particularly in instances where the cyst-solid part ratio is low. The typical central scar can be only observed in 30% of cases, which is often accompanied by calcifications in the central scar. [39] (Figure 4.) SCNs display high signal intensity on T2-weighted images, particularly in the microcystic regions. T2-weighted sequences can outline the central scar and calcifications as hypointense elements. On the early phase sequences, hypervascular enhancement can be seen. [39]

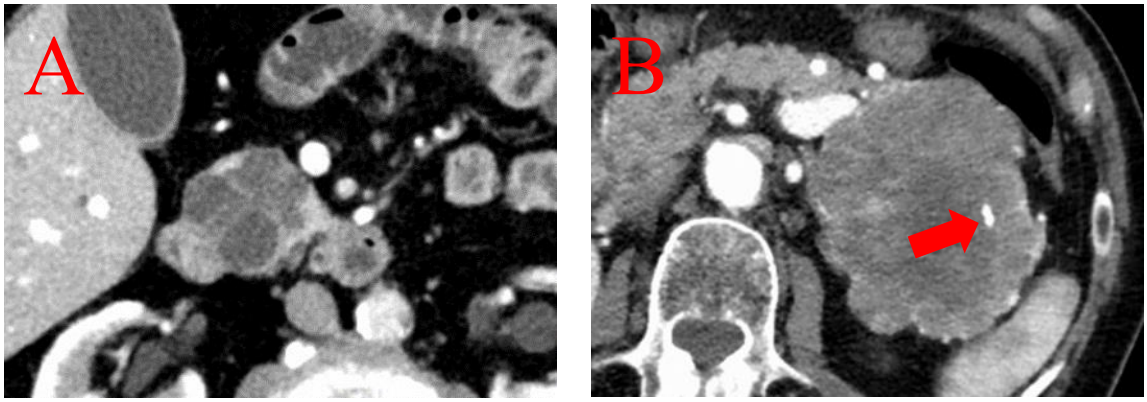

Figure 4. *Axial reconstructions of portal venous phase CT series of a macrocystic (A) and a microcystic (B) serous cystic neoplasm (SCN). Due to the submillimeter diameter of the cysts, the microcystic subtype can mimic solid tumors on contrast-enhanced CTs, however the center calcification (arrow) is characteristic for SCN. (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.3.3.4 Intraductal papillary cystic neoplasm

Main duct type IPMNs can manifest as focal or diffuse dilation of the main pancreatic duct. Side branch type may show an unilocular cystic (sometimes multicystic) mass, on MRI it is usually displaying heightened T2 signal intensity or as a conglomeration of cysts near to the main duct. [39] Radiologically, prominent dilation exceeding 6 mm of the main pancreatic duct is a common feature, often extending into secondary branches. Solid intraluminal nodules or ductal wall, coupled with calcifications, contributes to the characteristic radiographic profile. Pancreatic enlargement or atrophy can be accompanied. [48, 73] Enhancing irregular septa or nodules within the lesion could imply the presence of adenocarcinoma. The demonstration of communication with the main pancreatic duct on CT could be facilitated using multiplanar or curved planar reconstruction. [39] MRI with MRCP play a crucial role in the comprehensive characterization of IPMNs. The MRCP illustrates most accurately the communication with the pancreatic duct. [39]

1.3.3.5 EUS – FNA augmented with intracystic biomarkers

EUS is a semi-invasive modality although having the greatest capacity to visualize the lesions. EUS can offer valuable insights into the internal attributes of cystic lesions. (Figure 5.) It may offer the best ability to visualize the communication with the main pancreatic duct and the presence of intracystic nodules. [39] In the presence of mural nodules contrast enhanced EUS (CE-EUS) can be also performed. Malignant transformation is suspected if there is hyperenhancement of the mural nodule or septum on CE-EUS. [31] When CT or MRI imaging is uncertain, EUS-FNA improves the diagnostic performance by distinguishing between malignant and benign PCN as well as mucinous and non-mucinous PCN. [31] However, obtaining fluid from the microcystic variant can pose challenges in contrast to the oligocystic variant. The oligocystic type is considerably harder to diagnose, given that its radiological attributes share commonalities with MCNs and BD-IPMNs. In scenarios characterized by such uncertainty in the diagnosis, the diagnosis of an oligocystic SCN can be supported by the presence of small peripheral cysts visible by EUS and the evidence of low CEA levels. [48, 74] Consequently, EUS-guided biopsy and fluid aspiration may strongly support the diagnosis. [48, 75] The diagnostic sensitivity and specificity of cyst fluid analysis ranges

between approximately 57% to 94% and 85% to 97%, respectively. [39, 76, 77, 78] (Table 2.)

Table 2. *The intracystic amylase, CEA and serum CA19-9 levels in the different type of lesions* [31,39]

	Intracystic amylase (>250 IU/l)	**Intracystic CEA (>192ng/ml)**	**Serum CA19-9 (>37U/ml)**
Pseudocyst	elevated	not elevated	not elevated
SCN	not elevated	not elevated	not elevated
MCN	usually not elevated	elevated	if elevated, malignancy is suspected
IPMN	can be elevated		

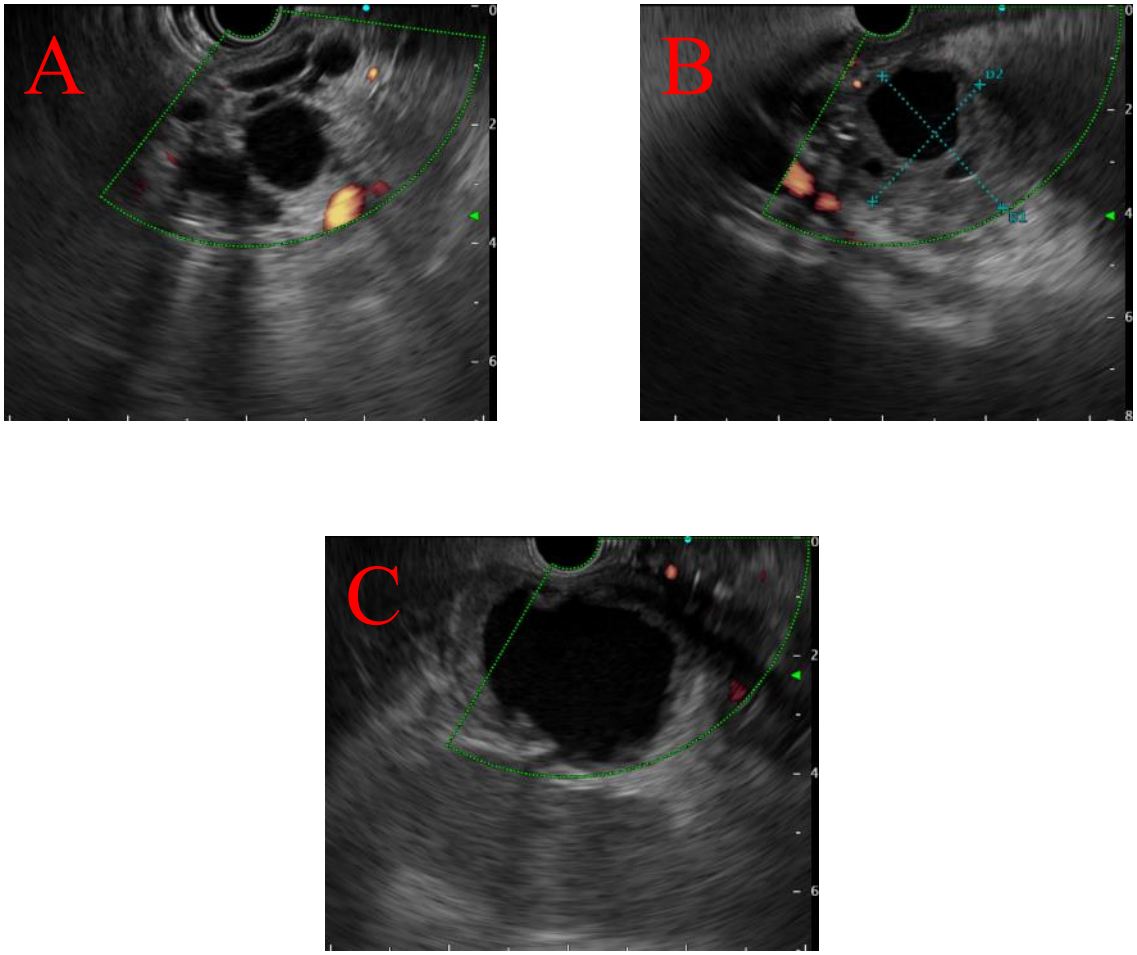

Figure 5. *Echoendoscopic image of mucinous cystic neoplasm (MCN) (A), serous cystic neoplasm (SCN) (B) and pseudocyst (C). (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

1.3.4 Management and treatment of PCNs

Few subjects within the realm of medicine evoke as much controversy as the assessment and treatment of patients afflicted with cystic neoplasms. [35] The approaches and current guidelines to managing PCNs has undergone multiple revisions. [31, 79, 62] The objective is to avoid benign lesions from unnecessary surgical procedures, while also ensuring that patients with (pre)malignant conditions are not missing the proper resection. Surgical intervention presents an opportunity for primary prevention of pancreatic cancer or its early-stage management. Nevertheless, suboptimal patient stratification may result in subjecting a substantial number of individuals to the considerable consequences of a major pancreatic resection. [33, 31, 40, 80] Certain incidental pancreatic cysts, including IPMNs or MCNs, possess malignant or premalignant characteristics, regardless of their size. Hence, there is no agreement whether surgical intervention or imaging-based surveillance should be considered for the optimal management strategy. [31, 36] The limited accuracy of preoperative imaging techniques creates challenges when making clinical decisions. Surgical indications for PCNs are restricted to cases involving symptomatic lesions or those suspected to be malignant or having a high potential for malignancy. [31, 81]

The main objective of the management in the cases of MCN is to screen patients without worrisome features thus avoiding unnecessary surgical resection. [48] At present, surgical resection constitutes the therapeutic approach. The resection is preferable in young patients where otherwise life-long screening would be needed. Resection of MCNs, which is mainly located in the body and tail of the pancreas, is associated with minimal mortality and limited morbidity in experienced high-volume centers. MCNs do not need post-surgical follow up unlike IPMNs do unless there is evidence of invasive cancer. [48, 62] The prognosis of invasive mucinous cystadenocarcinoma is good, the 5-year survival rate is 63%. However, in older patients (>50years) and if the invasive carcinoma is accompanied by either diffuse intracapsular infiltration or peritumoral invasion it is less favorable. [46, 48, 49]

Given the benign nature of SCN, therapeutic indication, involving surgical resection, should be indicated upon the presence of symptoms. Patients managed conservatively may warrant periodic imaging follow-up to detect rapid neoplastic growth. [48, 55, 60]

Despite the endeavors in researches, alongside numerous published studies, the management of PCNs still remains a subject of ongoing debate and is influenced by four primary sets of guidelines: the International Guidelines of the International Association of Pancreatology (IAP) (2006, 2012, 2016) [33, 82]; the European evidence-based guidelines by the European Society of Gastrointestinal Endoscopy (ESGE) issued in 2013 and updated in 2017 [31, 33]; the 2015 guideline provided by the American Gastroenterological Association (AGA) [33, 83] and the 2023 Kyoto guideline. [83] While these guidelines do exhibit certain commonalities, they also exhibit significant disparities in terms of patient management recommendations. Additionally, it is worth noting that these recommendations are largely grounded in expert opinions and rely on relatively weak scientific evidence, often derived from studies with notable selection biases. [33]

1.3.5 Software analysis tools

The accurate preoperative differentiation between benign and malignant (pre-malignant) lesions is critical. Imaging diagnostic tools are extensively used such as EUS, CT, and MRI to gain radiologic insights. CT has become the first-choice imaging modality to gain high-resolution cross-sectional images of the pancreas. [41, 85, 86] Unfortunately, achieving accurate classification of PCNs through manual assessment of radiological images continues to stay difficult, even for the most experienced radiologist. [41, 87] Prior investigations have indicated that the clinical diagnostic precision for benign pancreatic cystic lesion is unsatisfactory, leading to a situation where over fifty percent of patients receive unnecessary pancreatic resection instead of screening, follow-up and conservative management. [41, 66, 67, 81] Nowadays, the development of data analysis and computer-aided calculation methods, offers supplementary insights for radiologists. Wide range of machine learning algorithms can be constructed, enhancing the identification or differentiation of various tumors. Numerous algorithms have been developed for supplement the tumor diagnosis in diverse organs like the thyroid, lung, breast and brain. [41, 88] Investigations concerning PCNs and CT characteristics, including parameters such as tumor dimensions, cyst numbers, and the identification of calcifications are predominantly based on manual assessments. [41, 87] This primarily depends on the expertise of radiologists and neglects a great size of image data including

morphological characteristics, textural attributes, and intensity variations. Radiomics are a response to this challenge, they relate to the automated extraction and analysis of quantitative features from medical images, facilitating the development of algorithms for discrimination between diverse tumor types or predicting even survival outcomes. [41, 89]

1.4. Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

1.4.1. The different types of fluid collections

Acute pancreatitis is one of the most common diseases of the gastrointestinal tract that requires acute hospitalization and despite special care is still associated with significant morbidity and mortality.

The most severe local complications of pancreatitis include acute pancreatic fluid collection (APFC), pancreatic pseudocyst, acute necrotic collection (ANC), and walled-off pancreatic necrosis (WON). [90].

In the revised Atlanta classification [90], an essential differentiation was made between collections comprised solely of fluid and those developed due to necrosis. Necrotic fluid collections may contain variable amount of solid components (debris) and also fluid. As a complication of acute pancreatitis, three distinct entities of fluid collections can manifest:

1) APFC
2) Pancreatic pseudocyst, typically appearing after a duration of more than four weeks from the onset of pancreatitis.
3) Necrotic fluid collections can present in two forms:
    a. ANC, observed in the early phase before demarcation.
    b. WON, encompassed by a radiologically identifiable capsule, which infrequently develops before four weeks from the initiation of pancreatitis.

1.4.1.1 Acute pancreatic fluid collection

Fluid collections commonly occur in the initial stages of pancreatitis [90, 91]. On contrast enhanced CT, APFCs are usually homogenous fluid collections within the retroperitoneal space delineated by normal fascial planes without a well-defined wall. Furthermore, APFCs may present as multiple collections. Most APFCs commonly remain aseptic and tend to undergo spontaneous resolution without the need for intervention. [90, 91, 92] In cases where a localized APFC persists beyond four weeks, it may progress into a pancreatic pseudocyst, although this outcome is rare. Asymptomatic APFCs developed due to acute pancreatitis do not need treatment and do not indicate severe acute pancreatitis, they fall into the moderately severe category. [90] Additionally, APFCs can also develop due to various etiologies such as inflammatory processes triggered by factors such as trauma, surgical interventions, malignancy, transplantation, or obstruction of the pancreatic duct. [93, 94, 95, 96, 97]

1.4.1.2 Pancreatic pseudocyst

Pseudocysts are mainly located in the peripancreatic tissues, with partial or complete intrapancreatic involvement. The pseudocyst is characterized by a well-defined wall and predominantly contains fluid with minimal to no presence of solid material. The diagnosis is generally made based on these morphologic criteria. [90]

Pseudocyst are estimated to complicate approximately 5% to 20% of patients affected by acute or chronic pancreatitis and can be associated with significant morbidity. [90, 93, 98, 99, 100, 101] The etiology of a pancreatic pseudocyst is thought to involve the disruption of the main pancreatic duct or its intra-pancreatic branches, without the concurrent presence of pancreatic parenchymal necrosis. This theory proposes that the subsequent leakage of pancreatic juice leads to the formation of a persistent, localized fluid collection, typically occurring after a duration of more than four weeks. [90]

Majority of pseudocysts remain asymptomatic and do not require therapeutic intervention. Spontaneous regression of pseudocysts has been reported to occur in a variable range, approximately between 7% to 60%. [99] Drainage is recommended when persistent symptoms are present such as abdominal pain, luminal obstruction caused by the pseudocyst (e.g. gastric outlet obstruction, biliary obstruction) or when there is evidence of infection of fluid collection. [99, 100, 102] Pseudocysts are not associated with persistent pancreatitis, observation is advised due to the likelihood of spontaneous resolution. A standard observation period of 6 weeks is typically suggested before considering decompression. [99] (Figure 6.)

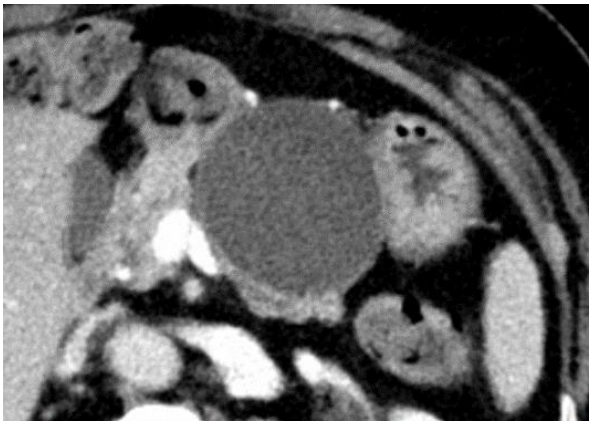

Figure 6. *Axial reconstructions of the portal venous phase CT series of a pseudocyst of a 75-year-old female after acute pancreatitis (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.4.1.3 Acute necrotic collection

Within the initial four weeks after acute pancreatitis, a collection containing varying proportions of fluid and necrotic material is classified as an ANC. The necrosis can affect the pancreatic parenchyma and/or peripancreatic tissues. The presence of an ANC may be associated with the disruption of the main pancreatic duct within the zone of parenchymal necrosis and can be susceptible to infection. Pancreatic necrosis complicates around 15% of pancreatitis, and within this subset, approximately 33% (16% to 47%) are further complicated by the occurrence of infected necrosis. [90, 93, 94]

In the initial weeks, differentiation between an APFC and an ANC can be challenging. Both types of collections may present as areas with fluid density at this early stage. However, as the disease progresses beyond the first week, the differentiation

between these two significant collections becomes more pronounced. Using imaging modalities such as MRI, US, or EUS may aid in confirming the presence of solid content within the collection. [90]

1.4.1.4 Walled-off pancreatic necrosis

WON is characterized by the presence of necrotic tissue enclosed within a wall of fibrotic tissue. (Figure 7.) It represents a developed, encapsulated collection of pancreatic and/or peripancreatic necrosis, typically maturing ≥4 weeks after the onset of acute necrotizing pancreatitis. Previously, this entity had been referred to by various suggested names, such as organized pancreatic necrosis, necroma [103], pancreatic sequestration [104], pseudocyst associated with necrosis [105], and subacute pancreatic necrosis. [106]

The differentiation between solid and liquid content on contrast enhanced CT may pose challenges, leading to potential misidentification of pancreatic/peripancreatic necrosis as a pancreatic pseudocyst. Additional imaging modalities such as MRI, US, or EUS may be utilized to achieve precise differentiation. [90]

While many acute PFCs tend to resolve spontaneously without intervention, pancreatic pseudocysts and WOPNs may necessitate intervention if they cause symptoms or complications like gastric outlet obstruction, biliary obstruction, infection, or rapid enlargement. [97, 107, 108]

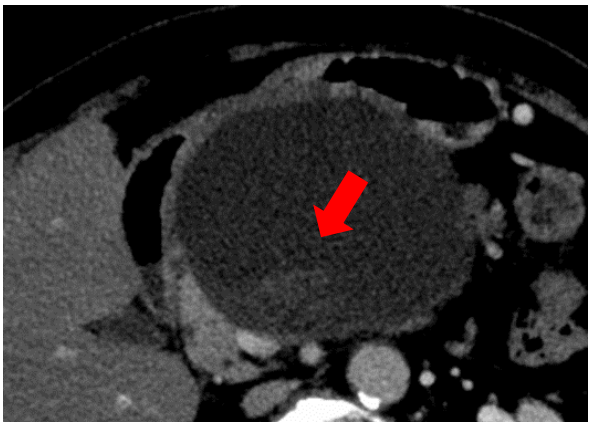

Figure 7. *Axial reconstructions of the portal venous phase CT series of a walled-off pancreatic necrosis (WON) in a 67-year-old female after acute necrotizing pancreatitis. The arrow indicates the necrotic tissue inside the well-demarcated WON. (Courtesy of Dr Ibolyka Dudás and Dr Bettina Budai, Medical Imaging Center, Semmelweis University)*

1.4.1.5 Infected necrosis

The diagnosis of infection, specifically infected necrosis, in cases of ANC or WON should be considered if presence of gas within the collection can be observed on contrast enhanced CT. Infected pancreatic/peripancreatic necrosis in acute pancreatitis represents a potentially life-threatening condition, with mortality up to 35%. [90, 99] In instances of uncertainty, FNA for pathology, microbiology and laboratory assessments can be performed; however, several studies have demonstrated that most patients can be managed effectively without the need for FNA and overall sampling, except when percutaneous drainage is integrated into the management protocol. [90, 109]

1.4.2. Management and diagnosis

The most effective diagnostic tool is imaging (CT or MRI), [107, 110] but EUS can also provide additional characterization of these collections. [107, 111] The indication and optimal timing for drainage have become subject to substantial debate in recent years. [107, 112, 113] Traditionally, pancreatic pseudocysts with a diameter ≥6 cm and/or persistence for ≥6 weeks were typically considered for drainage. [107, 114] However, recent investigations have suggested that prolonged observation can be both safe and effective, allowing for spontaneous resolution if the patient's clinical condition remains stable. [107, 115]

There is ongoing debate in the literature regarding the reliability of the 6-week cutoff, especially concerning larger pseudocysts (>4 cm in size) that may necessitate therapeutic intervention. In the context of chronic pancreatitis, pseudocyst may require drainage to relieve symptoms related to the presence of a space-occupying mass. Patients commonly experience a persistent and dull pain, furthermore there is a possibility of developing symptoms indicative of gastric outlet obstruction or jaundice due to compression of the bile duct. [99]

Nevertheless, some studies have proposed that a pseudocyst is unlikely to resolve spontaneously in the presence of chronic pancreatitis, a thick surrounding wall, pancreatic duct anomaly or a duration exceeding 6 weeks. [107, 113, 116] In cases where drainage becomes necessary, it is advisable to perform the procedure after 4 weeks to promote encapsulation and minimize potential adverse events. A notable study in 2011 demonstrated a correlation between the interval from hospital admission to intervention

for PFCs and mortality rates: (0 to 14 days: 56%; 14 to 29 days: 26%; and >29 days: 15%; $p<0.001$). [107, 117]

The ASGE issued guidelines to address the optimal approach. The drainage is generally recommended after 4 weeks to promote improved encapsulation and reduce the occurrence of adverse events following the procedure. However, it is important to note that this recommendation does not apply to infected collections, which mandate immediate drainage if suspected. [90, 102, 107]

1.4.3. Therapeutic approaches

PFCs can be managed through surgical, percutaneous, or endoscopic therapeutic ways. [96, 118, 119, 120] The median percentages of technical success, PFC resolution, complications, and recurrence in transmural pseudocyst drainage via endoscopic route were 93.8%, 87.5%, 16.9%, and 7.5%, respectively. [96, 118, 121, 122, 123]

Previously, the traditional approach to treat pancreatic pseudocysts was surgical intervention, which has demonstrated high efficacy. However, surgical procedures are associated with significant morbidity rate that range from 7% to 35% and a mortality rate of 6-10%. [99, 118]

Therefore, there has been a growing interest in exploring minimally invasive treatment options, such as (EUS-guided) endoscopic transmural drainage. [99] In recent times, a paradigm shift has occurred in the treatment due to evolving insights into pathophysiology and the advent of advanced technologies. This shift has driven a pronounced focus towards supporting minimally invasive strategies. Less invasive methodologies are initially pursued, with a careful escalation towards the more invasive modalities as dictated by the clinical progression. [93] Ultrasound or CT guided percutaneous aspiration have been explored as potential nonsurgical options. However, aspiration alone has been found to be ineffective, leading to a high recurrence rate of up to 71%. [99, 124] In response, continuous percutaneous drainage with indwelling drains has been employed to reduce the risk of recurrence. However, percutaneous drainage has its own set of challenges, including a complication rate ranging from 5% to 60%. [99] The percutaneous drainage also escalates the possibility to infections or the formation of a pancreatico-cutaneous fistula. [97, 108, 118, 125]

Due to recent technological advancements in technical infrastructure and increased experience have led to endoscopic drainage emerging as the preferred approach. Endoscopic intervention has several advantages, including cost-effectiveness, shorter hospitalization duration, equivalent clinical outcomes and comparable efficacy when compared to surgical cystogastrostomy. Consequently, the endoscopic drainage has gained recognition as a clinically viable, economically advantageous alternative minimally invasive substitute for surgical intervention. [97, 107, 108, 118, 126]

The endoscopic intervention involves the creation of a fistulous tract connecting the pseudocyst to either the gastric lumen (cystogastrotomy) or duodenal lumen (cystoduodenostomy). Following successful endoscopic access to the pseudocyst, continuous drainage is facilitated through the placement of a nasocystic catheter or a transmural stent. However, one of the limitations of endoscopic transmural drainage of pseudocysts is its relatively blind approach. The risk of perforation is notably increased, particularly in cases where there is no endoscopically visible intraluminal bulging to guide the procedure. Furthermore, endoscopic cystoduodenostomy or cystogastrostomy carries a significant risk of hemorrhage, with approximately 6% of cases. [99, 122, 127] EUS-guided drainage has become the first line option for the management of PFCs. Its clinical efficacy is high, comparable to surgical and percutaneous approaches, yet it comes with the advantage of lower morbidity and costs. With the guidance of EUS, the clinical success rate in draining PFCs stood at 89%, accompanied by a complication rate of 10% within a range of 0% to 26%. [118, 123] An evident superiority of EUS-guided drainage lies in its ability to effectively manage collections without endoluminal bulging, which sets it apart from non-EUS-guided techniques. [99, 128] EUS-guided drainage is not advised in the initial stages of collection formation due to the lack of a clearly demarcated cyst wall. Therefore, a thorough assessment of the type of collection is essential in determining the appropriate approach for drainage. [99] In situations where PFCs are characterized by multiple or multiloculated compartments, the endoscopic approach may not offer sufficient treatment and instead, surgical resection could become necessary. The endoscopic method might encounter difficulties in adequately draining all compartments of the PFC, potentially resulting in contamination and an elevated risk of infection if complete drainage of the cyst contents cannot be achieved. As a result, a surgical intervention may be deemed more appropriate in such complex cases. [99]

1.4.4. Endoscopic drainage with double pigtail stents and lumen-apposing metal stents.

EUS can secure the safe establishment of artificial fistulous tract connecting PFC with the gastrointestinal lumen. [96, 97, 183] The insertion of DPPS has emerged as a clinically effective and safe intervention within the evolving realm of therapeutic EUS. [100, 129] Recent custom engineered advancements have introduced LAMS with the goal of further optimizing therapeutic outcomes of PFCs, particularly WONs. LAMSs' key objective is to enhance the efficacy of necrotic content drainage while concurrently reduce the risks associated with perforation and peritoneal leakage. Randomized clinical trials comparing endoscopic and surgical modalities have consistently demonstrated results favoring the endoscopic approach. [99, 108, 126, 130] LAMS show exceptional advantages, including its robust diameter ranging from 10 to 20 mm, bi-flared flanges designed to avoid stent migration, and insertion as a one-step device, with electrocautery-tip without extra needle puncture, wire guidance, tract dilation, or fluoroscopic guidance. [100]

While transmural drainage alone is often sufficient for pseudocysts, direct endoscopic necrosectomy (DEN) as a step-up approach may be necessary to effectively address the necrotic tissue. [99] The larger diameter of LAMS not only facilitates efficient drainage but also allows the insertion of an endoscope into the WON cavity in order to make the DEN applicable, thus further enhancing the therapeutic approach. [99]

Studies have already showed the great efficacy and safety profile of LAMS in the management of pancreatic necrotic collections. [100, 131, 132] LAMS costs more compared to conventional plastic stents but need less interventions in the management of WON compared to DPPS. Moreover, the stent insertion could potentially lead to adverse events, necessitating unexpected endoscopic procedures, percutaneous drainage, or even surgical interventions. [100] However the DPPSs have a considerable risk of migration and due to their narrow lumen, multiple stent implantations and subsequent interventions might become necessary. [93, 97]

2. OBJECTIVES

2.1. Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

- The primary objective of our study was to assess the diagnostic accuracy of EUS in cases of suspected choledocholithiasis.
- Evaluate the diagnostic accuracy of the ASGE guideline.
- Investigate the diagnostic value of the predictive factors defined by the guideline.

2.2. Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

- The aim of our study was to analyze the EUS images of pancreatic cystic lesions using an image processing software.
- Find objective and quantitative attributions by the software assessment to distinguish between the PCNs with malignant potential and benign lesions.
- Measure the areas, the echogenicity, the inhomogeneity and density values of the different kind of pancreatic cystic lesions.

2.3. Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

- In this study, from 10 European tertiary centers, we sought to evaluate the efficacy and safety of EUS-guided drainage of PFCs.
- Evaluate the technical characteristics of transmural drainage.
- Compare the technical and clinical outcomes and adverse events of drainage with LAMS and DPPS.

3. METHODS

3.1. Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

3.1.1. Study design

The study was conducted at two high-volume centers, at the 1st Department of Surgery, Semmelweis University (legal predecessor of the Department of Surgery, Transplantation and Gastroenterology) and the Bács-Kiskun County Teaching Hospital in Kecskemét, between 2016 and 2018. All enrolled patients were adults (over 18 years) who had legal capacity and provided informed consent for both EUS and ERCP prior to the procedures. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

3.1.2. Inclusion and exclusion criteria

Inclusion criteria included patients diagnosed with cholecystolithiasis exhibiting typical right subcostal symptoms, abnormal liver laboratory function tests, and/or US findings indicative of choledocholithiasis, such as the presence of bile duct stones or bile duct dilatation.

Exclusion criteria were chronic liver disease, chronic pancreatitis, presence of gastrointestinal tumors or metastases, and contraindications for EUS and/or ERCP. Pregnant women and adolescents were also excluded from the study.

3.1.3. Study design, patients, EUS and ERCP procedures

To determine the presence of choledocholithiasis, following the „step-up" approach, all patients underwent initial EUS, using linear EUS devices. If choledocholithiasis was detected during EUS, subsequent ERCP was performed for the diagnostic confirmation and stone removal purposes. In cases where choledocholithiasis was not confirmed during EUS, the subsequent ERCP was not performed and a follow-up of 2 months was conducted, consisting of laboratory test and US. In the absence of symptom progression and with no observed changes in laboratory values or US during follow-up, the negative EUS result was considered reliable. In some cases, despite a

negative EUS finding, the ERCP was performed due to progression of clinical symptoms. With few exceptions, EUS and ERCP procedures were performed in consecutive manner during a single session.

The enrolled patients were classified into risk groups based on clinical predictors for choledocholithiasis defined by the modified ASGE recommendations of 2019 (Table 3.).

Table 3**.** *Predictors and likelihood groups of choledocholithiasis based on the ASGE guideline from 2019* [9]

ASGE, 2019
High probability
Presence of biliary stone on abdominal ultrasound, CT or MRI
or
Bilirubin >4mg/dl (68,4 µmol/l) and presence of dilated common bile duct (>6mm in the presence of intact gallbladder) on abdominal ultrasound, CT or MRI
or
Ascending cholangitis
Intermediate probability
Abnormal liver function test results
or
Age >55 years
or
Dilated common bile duct (>6mm in the presence of intact gallbladder) on abdominal ultrasound imaging

Both EUS and ERCP procedures were performed by an expert endoscopist with several years of experience on the field. All endoscopic examinations were conducted in prone position. The procedures were carried out under conscious sedation (midazolam and nalbuphine), with continuous monitoring of essential patient vital parameters, including pulse rate, oxygen saturation, and blood pressure.

EUS examinations were conducted using a linear echoendoscope (Olympus EU-ME2 GF-UCT180 and Fujifilm EG-530UT or EG-580UT, Tokyo, Japan). In addition to targeted investigations for bile duct stones, a quick orientation of the pancreatobiliary system was also performed. If choledocholithiasis was confirmed by EUS, ERCP was performed during the same session in the majority of cases. In some cases, the examinations were not feasible during the same session, so they were performed sequentially as previously arranged with the patient.

In the context of the ERCP procedure, endoscope was selected based on the examining practitioner (Olympus TJF-145 or TJF-180V and Fujifilm ED-530XT). The cannulation of the papilla of Vater was performed using a sphincterotome (Olympus KD-

301Q-0330). Following successful cannulation, biliary endoscopic sphincterotomy (EST) was performed. In certain cases where primary biliary cannulation was not feasible, precut sphincterotomy using a needle-knife sphincterotome (Olympus KD-10Q-1) was performed to facilitate successful cannulation. Subsequently, the cannulation access was maintained using a guide wire (Olympus VisiGlide). Stone removal was performed using balloon sweeping of the bile duct (Olympus B-V233P-A) or by using a Dormia basket (Olympus FG-22Q1).

Following ERCP, routine infusion therapy using balanced crystalloid solutions (Ringer's lactate) of 2000-3000ml was administered. Due to sedation, patients were observed and monitored temporarily in the recovery room. In instances where main pancreatic duct cannulation occurred during ERCP, a prophylactic plastic stent (PPS) was inserted to prevent post-ERCP pancreatitis and, all patients received a single rectal dose of 100mg Indomethacin after the procedure.

Routine laboratory tests were conducted on the first day following ERCP for monitoring and to exclude post-ERCP pancreatitis. PPS were removed after 3-5 days. Routine administration of antibiotics directly prior or during the endoscopic interventions was not provided unless specific indications warranted such treatment.

3.1.4. Statistical analysis

Data collection, analysis, and figure generation were performed using the IBM SPSS Statistics 25 software and Microsoft Office Excel. The assessment of normality for each continuous variable was conducted using the Shapiro-Wilk test. In instances where a normal distribution was observed, the Student's two-sample t-test was employed for intergroup comparisons. For continuous variables that deviated from a normal distribution, the Mann-Whitney U-test was utilized for comparative investigations. Categorical variables were characterized by specifying the number of elements in the corresponding category and calculating the percentage distribution. For statistical analyses, we utilized the $\chi 2$ test or, in cases of low (less than 5) expected values, the Fisher's exact test. All statistical tests were conducted assuming a two-tailed distribution, with a significance threshold set at $p < 0.05$.

3.2. Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

3.2.1. Study design, definitions, and endpoints

We conducted a single center study from January 2018 to June 2021 at the 1st Department of Surgery, Semmelweis University (legal predecessor of the Department of Surgery, Transplantation and Gastroenterology). EUS with the right indication was carried out in adult patients (age >18 years) with pancreatic cystic lesions with unknown etiology (including PCNs and pseudocysts) previously detected by CT, MRI, or US for further evaluation. FNA or FNB was performed if further differentiation was necessary. Three groups were created, based on the cytology (EUS-guided FNA or FNB with certain cytology results, questionable results were excluded) and/or the postoperative pathology results. The IPMNs and MCNs were classified as Non-SCN category as they both present with a higher risk of malignancy. The SCN group contained only SCN lesions, and the third group was comprised of the pseudocysts. Software image analysis was performed on the EUS images archived during the endoscopic examination. An open-source image processing software (FIJI) was used for image analyzing. [133] The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by Scientific and Research Ethics Committee of Medical Research Council of Hungary (approval number: ETT-TUKEB IV/1121-1/2020/EKU).

3.2.2. Inclusion and exclusion criteria

Patients were enrolled in the study in whom pancreatic cystic lesions of unknown etiology had been detected by cross-sectional imaging or US, and for further evaluation, EUS was indicated. Each patient provided informed consent for undergoing the EUS examination. All enrolled patients had available results of certain cytological sampling taken by EUS and/or postoperative pathology results of pancreatic resection of those who underwent subsequent surgery. All enrolled patients were adults (over 18 years) who had legal capacity, limited legal capacity, or were incapacitated and provided informed consent personally or through their legally authorized representatives.

Patients with clear etiology of the pancreatic cystic lesion, thus not requiring EUS examination for further identification, as well as those with uncertain/non-definitive

pathological or cytological results or patients who did not consent to the EUS examination, were excluded from the study. Furthermore, patients lacking archived EUS images, analyzable by software or whose image format did not adhere to the specified criteria were similarly excluded from the study.

3.2.3. EUS procedure

Each EUS was performed by an expert endoscopist with several years of experience. Prior to the procedure, patients underwent a 2-hour fluid fasting period and a 6-hour dietary restriction. Each patient was expected to have a recent laboratory test within the past three weeks, including a complete blood count and coagulation parameters. Tissue sample collection was performed exclusively where coagulation parameters were within the normal range.

The examinations were executed in prone position and under conscious sedation, with continuous monitoring of vital parameters such as blood pressure, heart rate, and oxygen saturation. Nasal oxygen supplementation was administered concurrently with sedation, employing low flow rates. Olympus EU-ME2 GF-UCT180 EUS instrument was used for the examinations.

Following the precise localization of the cystic lesion, sample acquisition was carried out for each enrolled patient in the study. Prior to puncture, the safe trajectory of the sampling needle was determined using the colour flow function of Doppler ultrasound, ensuring a clear path between the lesion and the working channel of the endoscope. For FNA, Cook Medical EchoTip Ultra type needle (19,22 or 25 gauge) was employed, while Cook Medical EchoTip ProCore or Covidien SharkCore needle was utilized for FNB procedures (22 or 25 gauge). In cases where cystic lesions of unknown etiology contained solid components, FNB sampling was prioritized. From the cystic components of the lesions, samples were collected using a specialized 10 or 20ml vacuum syringe attached to the sampling needle, thus using a vacuum technique for sample gaining. Samples were obtained from the solid components of the lesions using both vacuum and "slow-pull" techniques. The "slow-pull" technique involved gradually withdrawing the sheath from the sampling needle while simultaneously performing fan-like punctures in the lesion, allowing the desired tissue core to be retrieved into the sheath's place. The cyst fluid obtained by vacuum technique was transferred into serum

test tubes for subsequent laboratory and cytological analyses. In the laboratory evaluation, levels of intracystic amylase, glucose, and carcinoembryonic antigen (CEA) were quantified.

The tissue cylinders acquired by the slow-pull and vacuum techniques were fixed on slides and within test tubes containing formalin solution and subsequently forwarded for pathological and cytological analysis. Rapid on-site evaluation (ROSE) was not conducted for any patient case.

After the procedure, patients were observed in a recovery area for a few hours. Patients received a single intravenous infusion of 400mg ciprofloxacin as antibiotic prophylaxis after the cyst sampling, followed by a 2x500mg per os dosing for a duration of 5 days after discharge.

3.2.4. Image processing

The images of the lesions were taken and saved for further analysis during the EUS examination. The procedures were performed by the same expert endosonographist. All PCNs were assessed with the same ultrasound frequency (5 MHz) and the focus distance was also set to the same way. The pictures with the most worrisome features were taken and saved for further evaluation. More of the images were taken if the lesion could be also visualized from another position or angle with a different appearance. All the pictures were saved in the same resolution (1280x960) and in the same format (jpg.).

We performed the pixel to millimeter (mm) calibration of the images using a text file (.txt) format macro written in Microsoft Notepad:

$$run(\text{"8-bit"});$$
$$setTool(\text{"line"});$$
$$makeLine(1227, 310, 1227, 556);$$
$$run(\text{"}Set\ Scale\ldots\text{"}, \text{"}known = 20\ unit = mm\text{"});$$

Running the macro, automatically drew a 20mm long line next to the caliper of the EUS image and calibrated the pixel/mm based on the pixel length of the line and the known distance. To accelerate the image analysis, the macro immediately converted the image to 8-bit. Due to the calibration, 1 mm was equivalent to 12.3 pixels, and the 8-bit format meant 256 possible gray tonal values for each pixel.

The mean gray value of the lesions meant the mean of the selected areas pixels' gray value in an 8-bit image format which corresponded to the echogenicity of the lesions. The standard deviation of the lesions meant the standard deviation of the selected areas pixels' gray value in 8-bit image format which corresponded to the inhomogeneity of the lesions. The density was a standardized characteristics' value for the lesions. It meant the sum of the gray values of the pixels in the selected part, divided by the selected part's area value:

$$Density = \frac{\sum Gray\ values\ in\ the\ selected\ part}{Selected\ part's\ area}$$

The area values in mm2 were calculated based on the calibrated estimates. The image requirements were as follows: image saved in the correct format, EUS performed on 5 MHz, lesion well defined, all parts of the lesions assessable and no duplication image of the same lesion.

We specified the echogenicity of the lesions by measuring the grey value of the pixel inside the selected areas. Besides the entire lesion, its cystic and solid parts (e.g., intracystic septa, nodules, cystic wall) were also selected separately for assessment. The entire lesion area was selected manually, using the software's free hand selection feature. The cystic parts were selected semi-automatically with the software's tracing tool where a tolerance value could be set in advance. Selecting a pixel inside the cystic region after the correct tolerance settings, the software automatically also selected the surrounding pixels based on the preceding tolerance setting. The tolerance setting determined the permissible gray value difference between the selected pixel and the automatically selected surrounding ones. The values of the solid parts were calculated by a mathematical formula, during which the values of the cystic part(s) were subtracted from the values of the whole lesion. Thus, the solid parts (e.g., the cystic wall of the Pseudocysts or SCNs) could be determined and measured much more accurately than with the free hand selection feature.

To standardize the analyzes process, beside the cystic lesions, a predetermined area (three circles with a diameter of 5 mm each) of healthy pancreatic parenchyma was also selected for assessment. All of these selected areas' echogenicity showed no significant differences compared to each other's, therefore every echogenicity value of

the healthy pancreas originated from the same sample population. The exclusion criteria were as follows: unavailable postoperative pathology or unclear FNA/FNB cytology result; images saved in the wrong format; lesion not well-defined or not all parts of the lesion assessable.

3.2.5. Statistical analysis

GraphPad Prism, IBM SPSS Statistics 25 and Microsoft Office Excel software were used for the data evaluation. Normality tests (Anderson–Darling, D'Agostino and Pearson, Shapiro–Wilk, Kolmogorov–Smirnov) were performed to determine the samples' normality level. In cases of normal distribution, the independent samples t-test, otherwise the non-parametric independent test, was applied. Continuous variables were presented as mean ± standard deviation (SD) or median with range, as appropriate for the data distribution. Categorical variables were characterized by specifying the number of elements in the corresponding category and calculating the percentage distribution. For statistical analyses, we utilized the $\chi 2$ test or, in cases of low (less than 5) expected values, the Fisher's exact test. A p value < 0.05 was considered statistically significant.

3.3. Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

3.3.1. Study design, patients

This retrospective cohort study was conducted at 10 European tertiary hospitals located in 4 different European countries: 5 centers in Athens, (Greece); Milan, Foggia, and Verona (Italy); Zagreb (Croatia), and Budapest (Hungary). The study followed the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [134] for presenting the study data.

All patients provided written informed consent prior to the procedure. Patients were identified from a prospectively maintained database across each center, with all data being extracted and finally compiled into a main database. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by Scientific and Research Ethics Committee of Medical Research Council of Hungary (approval number: ETT-TUKEB 45680-2/2019/EKU).

Patients who met the revised Atlanta criteria [90] for PFC including either pancreatic pseudocyst or WON and underwent EUS-guided transmural drainage using either a lumen-apposing metal stent (LAMS) or double-pigtail plastic stent (DPPS) between June 2016 and December 2019 were included in this study. Eligibility was determined based on the clinical evaluation of symptoms and cross-sectional imaging (ultrasound, computed tomography, magnetic resonance imaging, or EUS) confirming the presence of a symptomatic PFC.

Exclusion criteria included patients below 18 years of age, those diagnosed with cystic neoplasias or known pancreatic malignancy and cases where follow-up data were unavailable.

3.3.2. Drainage procedure of PFCs

Patients were instructed to a pre-procedural fasting period of 6 hours. Prophylactic antibiotics were administered based on the clinical judgement of the endoscopist and in accordance with the institutional protocols, considering the specific type and dosage. Every procedure was performed by an expert endoscopist who had completed at least 100 EUS-guided transmural drainages. The procedures were conducted under monitored anesthesia and sedation was administered using fractionated doses of propofol or midazolam augmented with minor opioid agents as per standard institutional practices and individual patient needs. The echoendoscopes used in the study included Olympus models (GF-UCT140-AL5 or GF-UCT180 + EU-ME2 Premier Plus, EVIS EUS, Olympus Optical Co. – Europa, Hamburg, Germany) and Pentax models (FG-36UA or EG-3870UTK, connected with Hitachi Avius, PENTAX Europe GmbH, Hamburg, Germany). The puncture was carried out in a standardized approach as previously described. [135] The selection between the LAMS or DPPS was based on the endoscopist's assessment and clinical decision-making process. (Figure 8.)

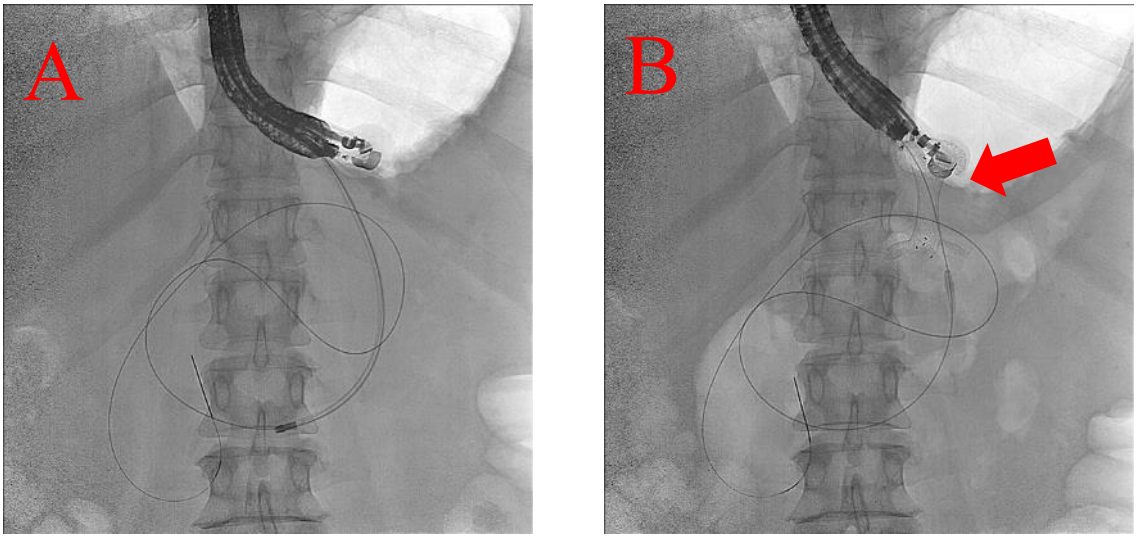

Figure 8. *LAMS implacement under fluoroscope. Echoendoscope with the cystotome and guidewire introduced into the walled-off pancreatic necrosis (WON) (A). Lumen-apposing metal stent (LAMS) (arrow) deployed through the guidewire into the WON. (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

3.3.3. PFC drainage with LAMS

After establishing the vascular-free pathway between the EUS probe and the PFC and confirming that the distance between the EUS probe and the PFC was ≤1cm, the LAMS (HOT AXIOS, Boston Scientific Corporation, Marlborough, MA, USA) was applied using the „free hand technique". The stent was placed into the PFC with cautery assistance, followed by the deployment of the distal and proximal rims under EUS and endoscopic visualization augmented by fluoroscopy (trimodal imaging), thereby achieving complete stent placement. All LAMSs employed in this study were exclusively of the HOT AXIOS variety. The LAMSs were removed upon achieving clinical success of drainage, as defined below. (Figure 9.)

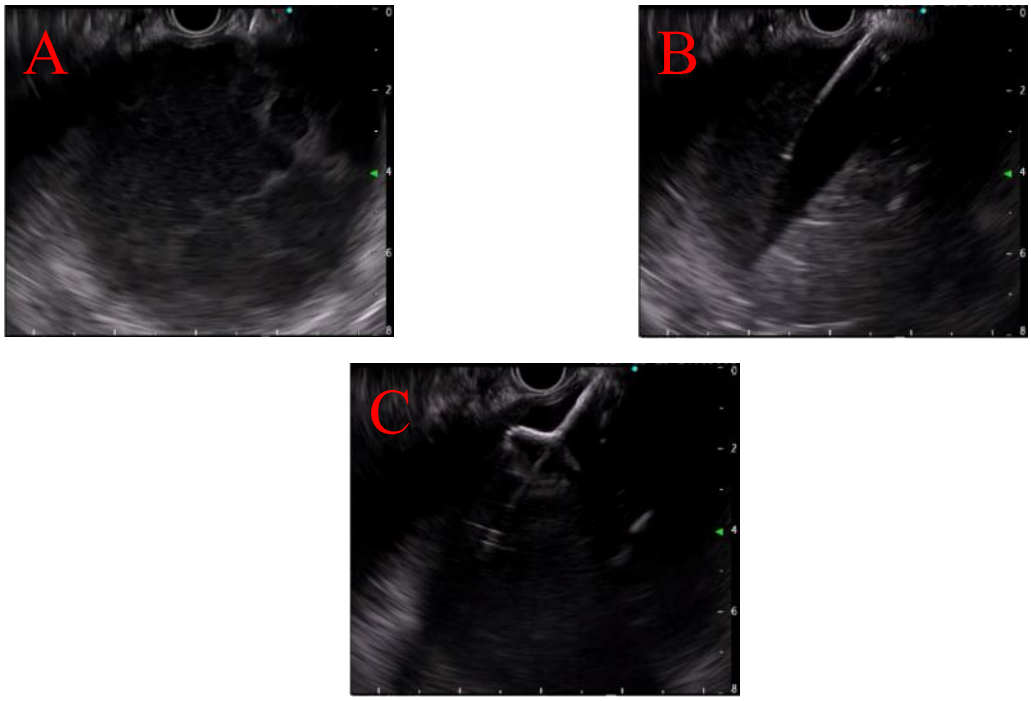

Figure 9. *Echoendoscope image of walled-off pancreatic necrosis (WON) (A); Electrocautery-enhanced delivery system introduced into the WON (B); the distal flange of the lumen-apposing metal stents (LAMS) (Hot Axios, Boston Scientific) deployed into the WON's cavity (C). (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

3.3.4. PFC drainage with DPPS

The PFC was punctured directly using a 10 Fr Cystotome (Cystotome TM, Cook Medical, Winston Salem, NC, USA) or the 8.5 Fr Cysto-Gastro-Set RU (ENDO-FLEX GmbH, Voerde, Niederrhein, Nordrhein-Westfalen, Germany) transmurally under the guidance of both ultrasound and fluoroscopy. Following the puncture, one or two guidewires were inserted into the cavity through the cystotome. Pneumatic dilation of the fistula was performed using a 6-, 8- or 10- mm ballon (MaxForce, Boston Scientific). Subsequently, one or two DPPS (5 cm length, 7 or 10 Fr in diameter) were deployed into the PFC. The DPPS were removed upon achieving clinical success of drainage, as defined below. (Figure 10.)

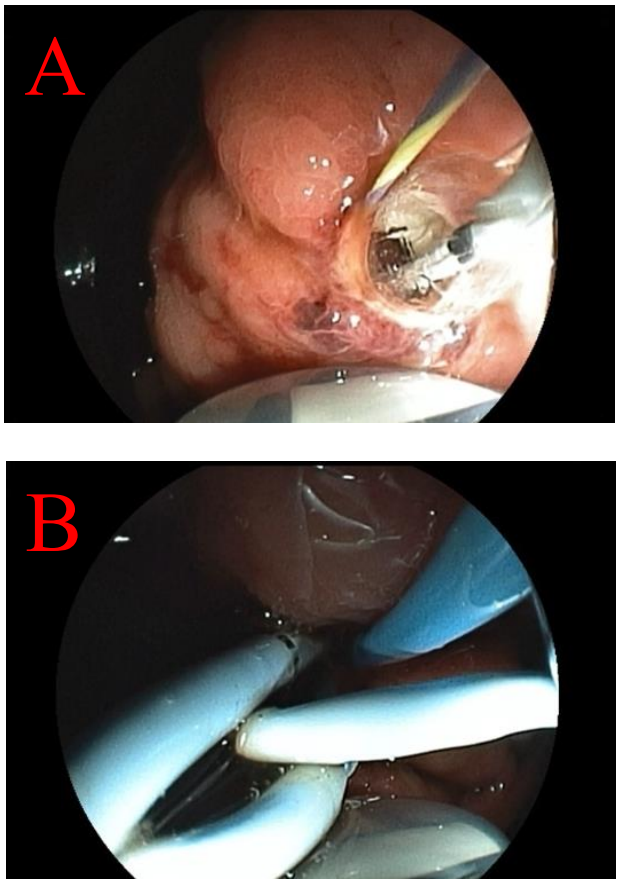

Figure 10. *Endoscopic image of ballon dilatation over the wire of the fistulous tract for pseudocyst access (A), and double pigtail plastic stents (DPPSs) placement after the dilatation. (B). (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

3.3.5. Study definitions and endpoints

Technical success was defined as the achievement of successful stent deployment, either with LAMS (Figure 11.) or at least one DPSS, creating a channel between the gastrointestinal tract and the PFC. Cases where the stent placement was accomplished in a single attempt were included only in the analysis. Clinical success was determined by the successful drainage of the PFC, characterized by a reduction in PFC size to 3 cm or less on cross-sectional imaging and resolution of PFC associated symptoms at the 6-month follow-up evaluation. [136, 137] Early adverse events were evaluated based on the severity grading outlined in the ASGE lexicon [138] and included adverse events that occurred within 30 days after the procedure.

The primary endpoint of the study aimed to assess the rates of technical success, clinical success, and early adverse events associated with the endoscopic drainage procedures for PFCs. The secondary endpoints included two aspects. First, a comparison was made between the LAMS and DPPS treatment groups in terms of technical success, clinical success, time required for PFC drainage, rate of early adverse events, complication rate during stent removal, and ease of stent placement using a visual scale ranging from 1 to 10. Moreover, another comparison was conducted between the two treatment groups specifically in the context of two types of PFCs, regarding technical success, clinical success, rate of early adverse events and complication rate during stent removal.

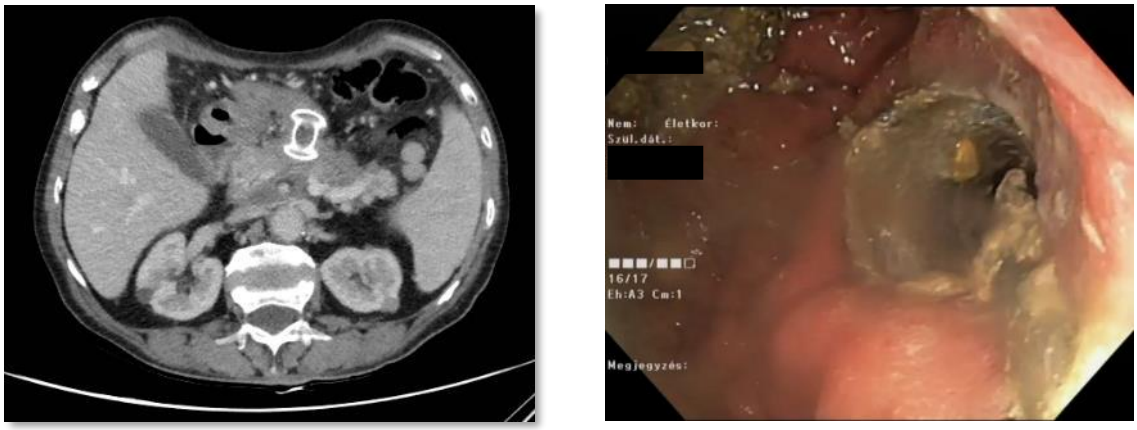

Figure 11. *Axial reconstruction of portal venous phase CT series of a LAMS (Hot Axios, Boston Scientific) inserted transmurally into the walled-off pancreatic necrosis (WON). Endoscopic image showing naso-cavital drain placed through the LAMS. Direct endoscopic necrosectomy was performed through the lumen-apposing metal stent (LAMS). (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

3.3.6. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with range, as appropriate for the data distribution. Categorical variables were represented as proportions along with their corresponding 95% confidence intervals (CIs). Statistical significance was defined as a p-value <0.05. All statistical analyses were performed using IBM SPSS Statistics 25.

4. RESULTS

4.1 Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

4.1.1 Patients' characteristics and research workflow

A total of 95 patients were enrolled to the study from two healthcare institutions. Among these patients, 78.9% (75/95) were female. The mean age of the female cohort was 61.3 ± 17.8 years, while the male cohort had a mean age of 60.9 ± 19.1 years.

Among the 95 patients, choledocholithiasis was assessed in 53 cases by EUS. (Figure 12.) In these cases, subsequent ERCP (53/53) consistently confirmed the diagnostic findings of the prior EUS examination, thus EUS exhibiting 100% accuracy. Stone extraction was successfully performed by ERCP in all cases.

A total of 73 ERCP were conducted, including 20 cases where the procedure was carried out despite the initial negative EUS findings. The clinical indication for these ERCPs included progressive dilatation of biliary ducts, escalating serum levels of obstructive enzymes and the persistence of suspicion of gallstones at US.

Among this cohort, ERCP confirmed the 'stone-free bile duct' diagnosis in 95% of cases (19/20), effectively validating the prior negative findings of the EUS. However, in one case, despite the previously negative EUS, ERCP revealed the presence of choledocholithiasis. Notably, in this patient whose gallbladder was removed earlier, approximately 7 weeks elapsed between the EUS and ERCP. Conversely, the remaining 19 patients presented with diverse pathologic conditions, including, sclerosis of the papilla of Vater (3/19), sphincter of Oddi dysfunction (4/19), juxtapapillary diverticulum (4/19), and biliary duct tumors (1/19). In 7 cases, no biliary abnormalities were detected. Sphincterotomy was performed in all cases except for the patient diagnosed with a bile duct tumor (19/20).

In 22 cases, a follow-up period of 2 months was carried out with a control laboratory assessment of serum obstructive and parenchymal enzyme levels after the initial negative EUS examination to confirm the accuracy of the EUS in the exclusion of choledocholithiasis. Among these 22 cases, 20 showed decreasing values during the course of control laboratory evaluations. In one case, the control laboratory results

exceeded the upper limit of normal values; however, these results showed a decreasing trend compared to the previous findings, and the patient remained asymptomatic, leading us to refrain from further intervention. In an additional case, the results remained elevated, prompting us to perform MRCP, which did not confirm the presence of bile duct stones. Given the patient's lack of symptoms, no further intervention was undertaken.

Considering the only single false negative case, the sensitivity of EUS in diagnosing choledocholithiasis in our study was 98%, with a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98%.

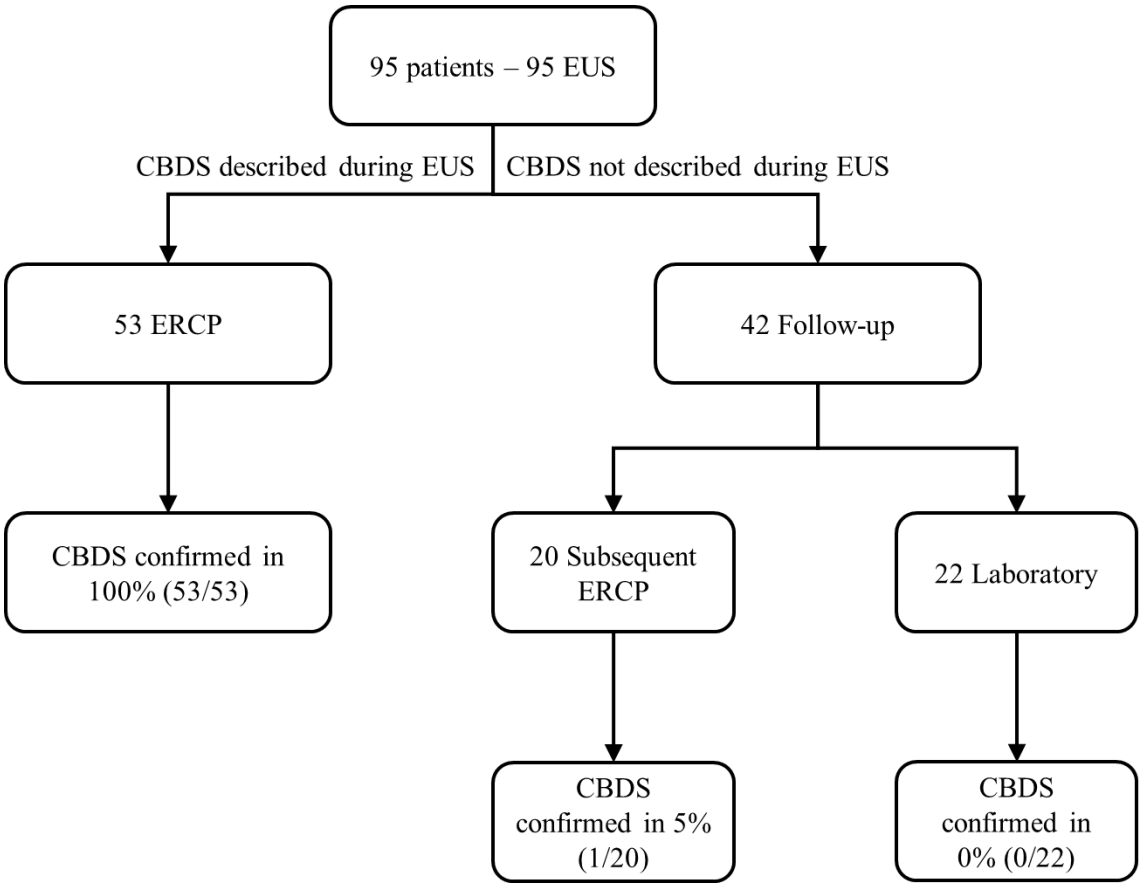

Figure 12. *Study flowchart (The figure was created by the author)*

4.1.2 Likelihood groups determined by the predictors

In accordance with the predictors defined by the ASGE 2019 modified guideline, our study classified 24 patients into the high likelihood group, while 71 patients were assigned to the intermediate likelihood group (no patients in low likelihood group). (Table 4.)

In the high likelihood group, EUS detected bile duct stone in 58% of patients (14/24). Among these 24 patients, 19 underwent subsequent ERCP, while 5 patients were subjected to a 2-month follow-up with control laboratory tests. ERCP confirmed the presence of bile duct stone in 15 patients, including the 1 case of a false-negative result, while no case of choledocholithiasis were identified during the follow-up assessments. Consequently, within the high likelihood group, choledocholithiasis was confirmed in 63% of cases (15/24).

In the intermediate likelihood group, EUS detected bile duct stone in 55% of patients (39/71). Out of the 71 patients, 54 underwent subsequent ERCP, and 17 patients were subjected to a 2-month follow-up. ERCP consistently confirmed the diagnosis made by the EUS in every case (39/39). Furthermore, in an additional 15 cases, ERCP did not confirm the presence of choledocholithiasis in alignment with the EUS findings. Among the 17 patients who underwent follow-up, no evidence of choledocholithiasis was subsequently established. As a result, within the intermediate probability group, choledocholithiasis was confirmed in 55% of cases (39/71).

Table 4. *The distribution of predictors in the likelihood groups*

Predictors	EUS (n=95, all patients)		ERCP (n=73)	
	High likelihood group (n=24)	Intermediate likelihood group (n=71)	High likelihood group (n=19)	Intermediate likelihood group (n=54)
CBDS on US/cross-sectional imaging	66% (16/24)	0% (0/71%)	63% (12/19)	0% (0/54)
Clinical ascending cholangitis	0% (0/24)	0% (0/71)	0% (0/19)	0% (0/54)
Total bilirubin >68.4 µmol/l (4 mg/dl)	71% (17/24)	0% (0/71)	84% (16/19)	0% (0/54)
Dilated common bile duct on US/cross-sectional imaging	58% (14/24)	24% (17/71)	53% (10/19)	24% (13/54)
Total bilirubin level 30.8-68.4 µmol/l (1.8-4 mg/dl)	0% (0/24)	23% (16/71)	0% (0/19)	22% (12/54)
Abnormal liver biochemical test other than bilirubin	58% (14/24)	77% (55/71)	53% (10/19)	74% (40/54)
Age >55 year	63% (15/24)	68% (48/71)	63% (12/19)	65% (35/54)

4.1.3 Common bile duct stone diagnosed by endoscopic ultrasound in the likelihood groups

In accordance with the ASGE 2019 modified guidelines, our study observed bile duct stones in 63% of patients in the high likelihood group and 55% of patients in the intermediate likelihood group. (Figure 13.)

In the high probability group, there was no statistically significant difference in the prevalence of choledocholithiasis when compared to the intermediate likelihood group (*p=0.517*). Correspondingly, the EUS did not exhibit a statistically significant difference in its ability to detect bile duct stones (*p=0.720*).

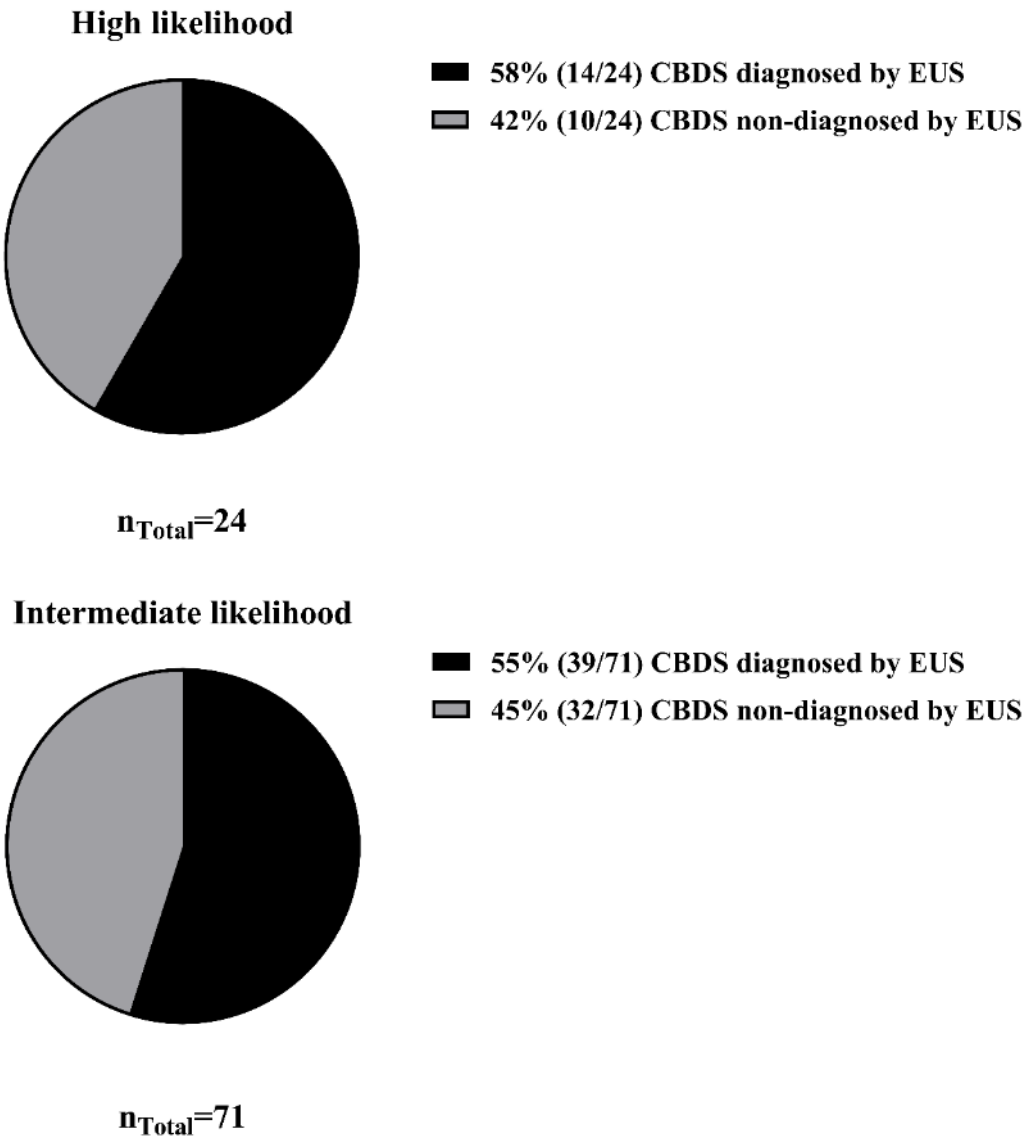

Figure 13. *Common bile duct stone detected by EUS in the likelihood groups (The figure was created by the author)*

4.1.4 Common bile duct stone confirmed by ERCP in the likelihood groups

Regarding the 73 ERCP procedures, there was no statistically significant difference in the number of confirmed cases of choledocholithiasis between the high and intermediate likelihood groups (*p=0.565*). (Figure 14.)

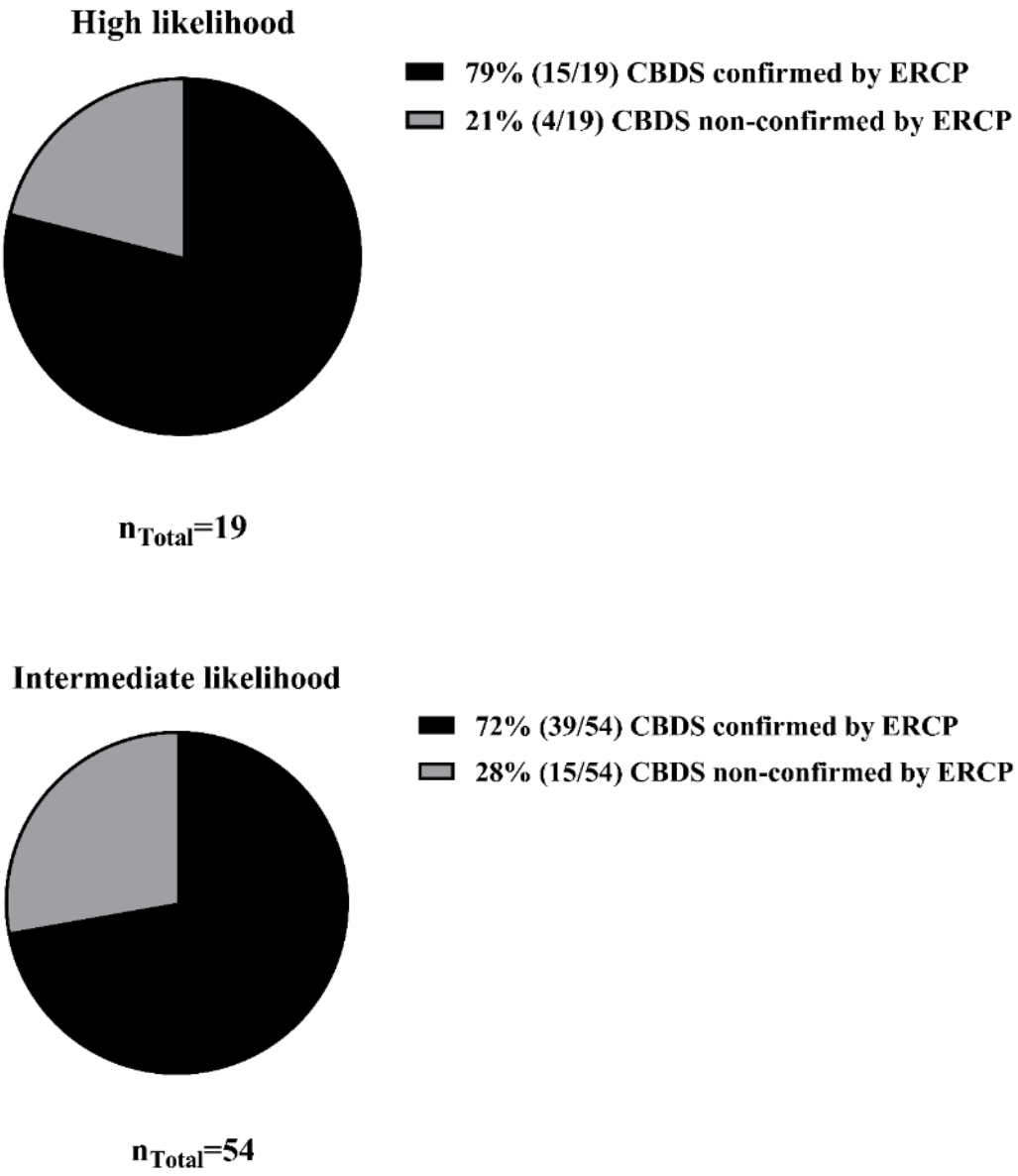

Figure 14. *Common bile duct stone confirmed by ERCP in the likelihood groups. (The figure was created by the author)*

4.1.5 Serum liver enzyme levels' assessments

Among all patients (95), none of the laboratory parameters (seBi, GOT, GPT, GGT, and ALP) demonstrated any correlation with the presence of choledocholithiasis. In other words, no significant differences were observed between the groups of patients with and without biliary stones for any of these parameters. The highest sensitivity for detecting bile duct stone was exhibited by ALP (75%) and GGT (82%), while total bilirubin had the highest specificity (66%). (Figure 15.)

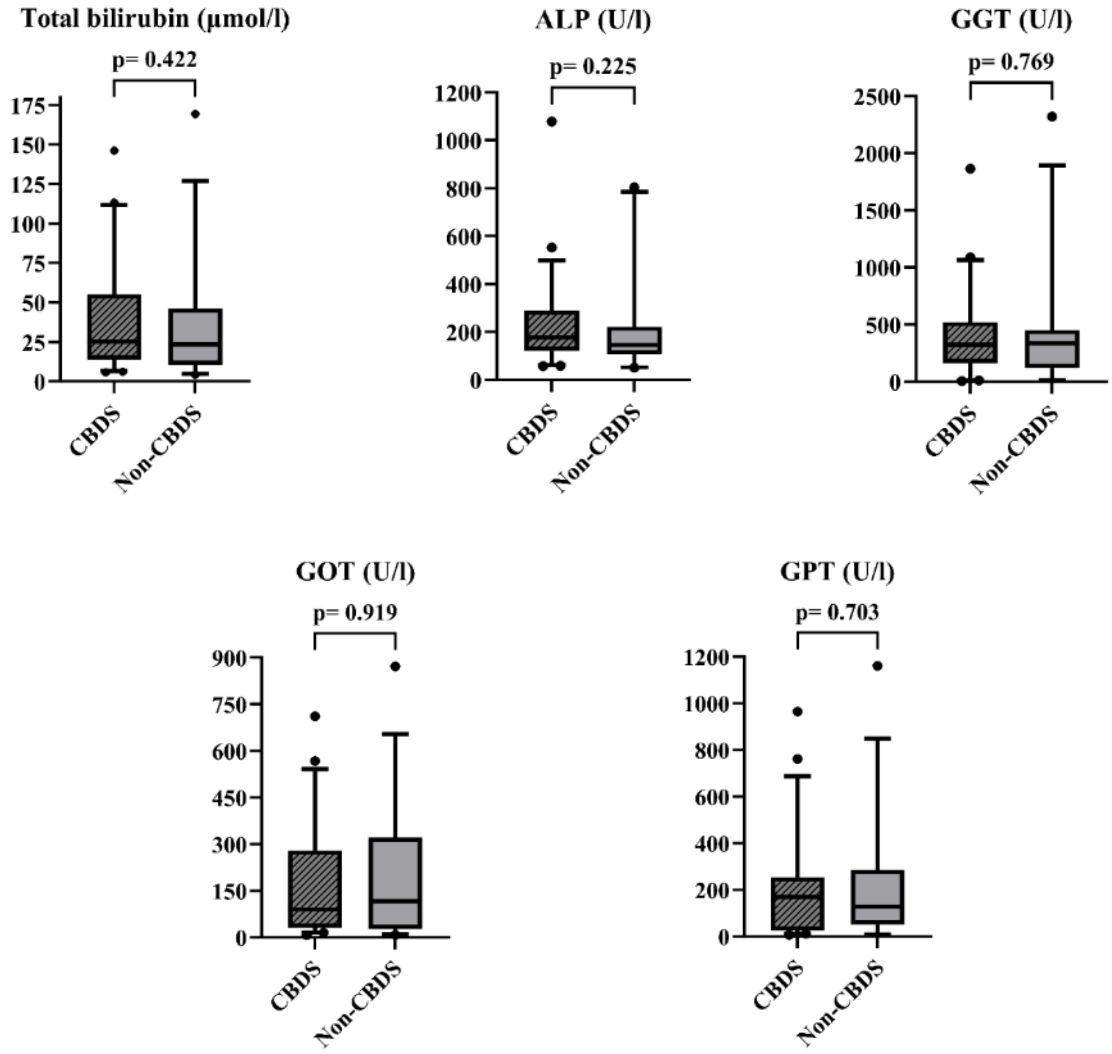

Figure 15. *Serum liver enzyme levels in patients with and without choledocholithiasis (with outliner values; the figure was created by the author)*

4.1.6 The performance of transabdominal ultrasound in the diagnosis of choledocholithiasis

In the subset of 54 cases, which were confirmed to have bile duct stones via ERCP, EUS detected (Figure 16.) a significantly higher rate of choledocholithiasis than US (53/54 vs. 8/54, $p<0.0005$). US of patients with intact gallbladders showed dilated bile duct in 53% of cases with choledocholithiasis which was confirmed subsequently; this percentage did not show statistically significant difference from the rate of bile duct dilation seen in patients without choledocholithiasis (46%, $p=0.6$).

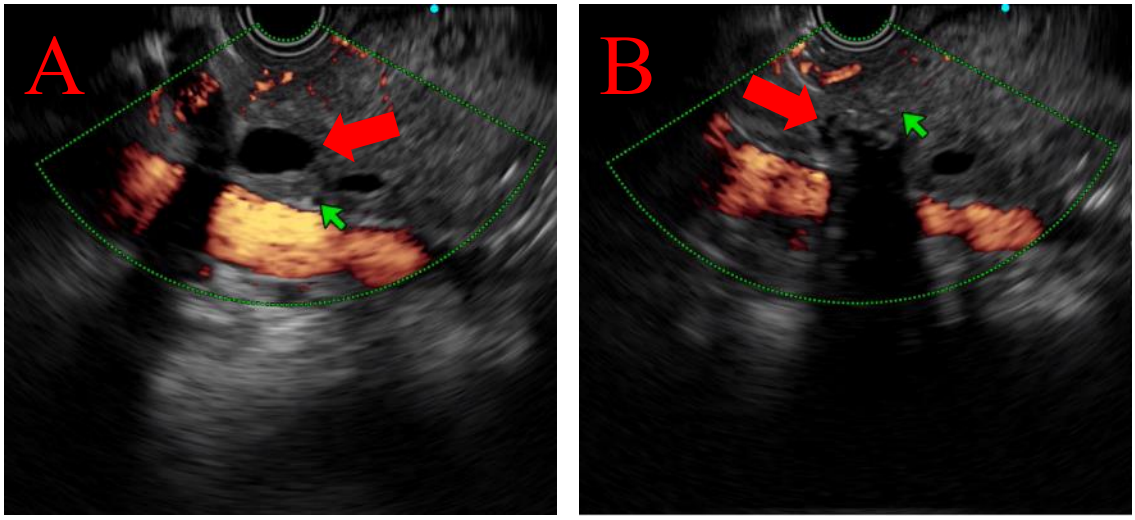

Figure 16. *Echoendoscopic images of the common bile duct (red arrow) without (A) and with (B) a bile duct stone. (The figure was created by the author from the database of the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University)*

4.2 Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

4.2.1 Study design and patients' characteristics

"During the observed time, 234 patients with suspected PCN or pseudocysts underwent EUS examination. The certain cytology results from FNA/FNB sampling and the postoperative pathology results were available in 75 patients. A total of 170 images were processed by the image analyzing software. In the SCN group, 30 images (11 patients) met the requirements for the software analysis (described in the Methods section), while in the Non-SCN group 81 images (32 patients) and in the Pseudocyst group 59 images (32 patients) could be assessed, respectively (Figure 17.).[139]

The mean age of the patients in the SCN, Non-SCN and the Pseudocyst groups were 59.4 ± 20.1, 61.8 ± 11.5 and 63.3 ± 13.1 years, respectively. In the SCN group 82% (9/11) of the patients were female, while in the Non-SCN and Pseudocyst groups 72% (23/32) and 63% (20/32), respectively. There were no significant differences between the groups in terms of age and gender." [139]

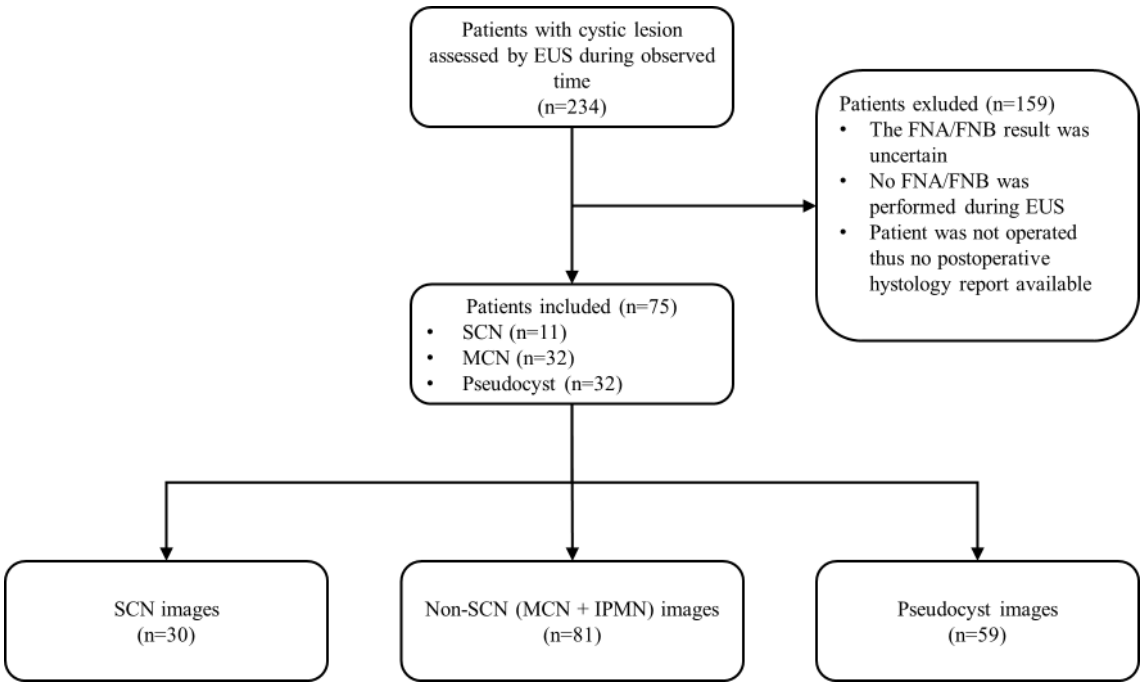

Figure 17. *Patients and study flowchart (The figure was created by the author) [139]*

4.2.2 The size, area ratio values and number of cystic lobules

"The whole lesions' mean sizes were 415.8±64.2mm2, 433.2±47.4mm2 and 590.4±77.6mm2, respectively, in the SCN, Non-SCN and the Pseudocyst groups. There was no significant difference between the SCN, Non-SCN and the Pseudocyst groups in terms of the lesion's size. The cystic parts' mean size was 116.8 ± 25.4mm2, 74.9 ± 14.1mm2 and 324.1 ± 55.8mm2, respectively, in the SCN, Non-SCN and the Pseudocyst groups. In the Non-SCN group, the cystic parts' areas were significantly smaller than in the SCN or the Pseudocyst groups (p=0.013 and p< 0.0005, respectively). (Figure 18.)*"* [139]

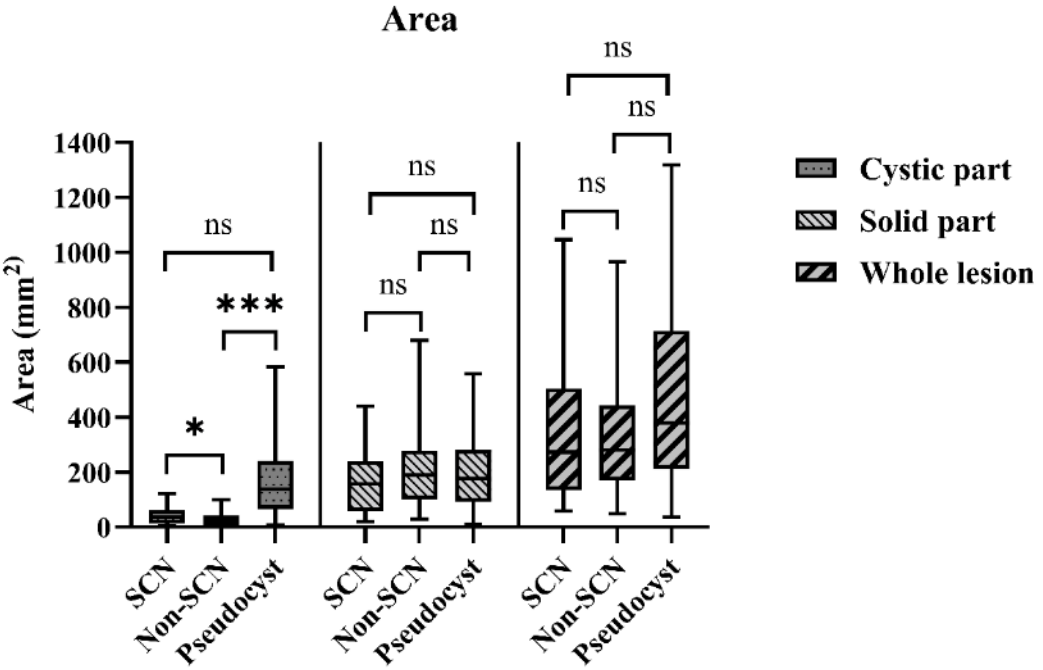

Figure 18. *Area values of the different parts in the groups (without outliner values; **p<0.005, ***p<0.0005, ns=non-significant; the figure was created by the author) [139]*

"The mean number of cystic lobules of the lesions was 2.1 in the SCN group, 2.4 in the Non-SCN and 1.2 in the Pseudocyst groups. There was no significant difference between the SCN and the Non-SCN groups, but in the Pseudocyst group the lesions had significantly fewer cystic parts, compared to the other groups ($p < 0.0005$) The mean value of the area ratio, which meant the proportion of the cystic part to the whole lesion was 57%, 39% and 61%, respectively, in the SCN, Non-SCN and the Pseudocyst groups. There was no significant difference between the SCN and Pseudocysts groups, but the Non-SCN group's area ratio was significantly lower than the SCN and Pseudocyst group's area ($p < 0.0005$). [139]

The mean echogenicity of the healthy pancreas parenchyma was 68.9±10.4, 68.3±11.3 and 69.4 ± 11.1, respectively, in the SCN, Non-SCN and Pseudocyst groups. There was no significant difference between the groups. (Table 5.)*"* [139]

Table 5. *Values of assessed attributions based on cystic lesions [139]*

Groups		Pseudocyst	SCN	Non-SCN
Number of images (n)		59	30	81
CT/MRI performed before EUS		100%	100%	100%
EUS guided biopsy/postoperative histology		75%/25%	75%/25%	44%/56%
Multidisciplinary team decision on diagnosis		100%	100%	100%
Echogenicity of healthy pancreatic parenchyma		69.4 ± 11.1 SD	68.9 ± 10.4 SD	68.3 ± 11.3 SD
Number of cystic lobules (n)		1.2	2.1	2.4
Area ratio		61%	57%	39%
Area (mm2)	Cystic part	324.1 ± 55.8	116.8 ± 25.4	74.9 ± 14.1
	Solid part	196.1 ± 131.6	168.2 ± 122.5	248.5 ± 199.9
	Whole lesion	590.4 ± 77.6	415.8 ± 64.2	433.2 ± 47.4
Echogenicity	Cystic part	7.5 ± 0.7	9.7 ± 0.7	11.1 ± 0.4
	Solid part	40.7 ± 1.6	31.4 ± 1.2	39.0 ± 1.2
	Whole lesion	19.8 ± 0.9	18.8 ± 1.2	27.8 ± 0.9
Inhomogeneity	Cystic part	7.1 ± 0.6	7.1 ± 0.7	6.9 ± 0.3
	Solid part	24.3 ± 1.1	16.1 ± 0.7	21.1 ± 0.6
	Whole lesion	22.6 ± 0.8	16.6 ± 0.7	22.3 ± 0.6
Density (∑gray values/mm2)	Cystic part	1127.3/mm2 ± 107.1	1461.4/mm2 ± 117.0	1668.6/mm2 ± 67.5
	Solid part	6117.9/mm2 ± 25.6	4737.6/mm2 ± 194.6	5875.0/mm2 ± 183.0
	Whole lesion	2981.6/mm2 ± 144.5	2833.8/mm2 ± 192.6	4186.6/mm2 ± 135.6

4.2.3 The echogenicity assessment of the cystic lesions

"The mean gray value of the whole lesions was 18.8 ± 1.2, 27.8 ± 0.9 and 19.8 ± 0.9, respectively, in the SCN, Non-SCN and Pseudocyst groups. The mean gray value in the Non-SCN group was significantly higher ($p < 0.0005$) compared to the other groups. There was no significant difference between the SCN and the Pseudocyst groups. The mean gray value of the cystic parts was 9.7 ± 0.7, 11.1 ± 0.4 and 7.5 ± 0.7, respectively, in the SCN, Non-SCN and Pseudocyst groups. In the Pseudocyst group, the mean gray value of the cystic parts was significantly lower than in the Non-SCN ($p < 0.0005$) and in the SCN ($p = 0.007$) groups. The mean gray value of the solid parts (intracystic septa, mural nodules, cystic walls) was higher in the Non-SCN (39.0 ± 1.2) and in the Pseudocyst (40.7 ± 1.6) groups than in the SCN group (31.4 ± 1.2). There was no significant difference between the Non-SCN and Pseudocyst groups, but in the SCN group, the cystic mean gray value was significantly lower compared to the Non-SCN ($p = 0.0009$) and the Pseudocyst ($p < 0.0017$) groups (Figures 19.)*."* [139]

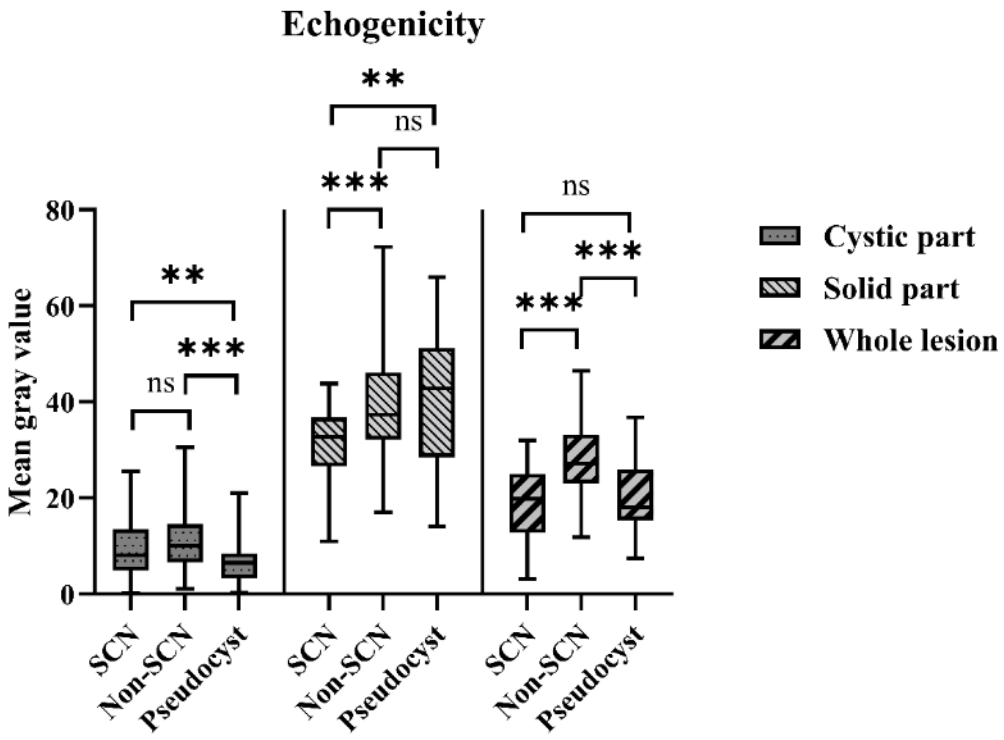

Figure 19. *Echogenicity values of the different parts in the groups (without outliner values; **p<0.005, ***p<0.0005, ns=non-significant*; the figure was created by the author*)* [139]

4.2.4 The inhomogeneity values of cystic lesions and its' parts

"The inhomogeneity value of the whole lesion was 16.6 ± 0.7 in the SCN, 22.3 ± 0.6 in the Non-SCN and 22.6 ± 0.8 in the Pseudocyst group. The inhomogeneity value was significantly higher in the Non-SCN ($p < 0.0005$) and in the Pseudocyst ($p < 0.0005$) groups than in the SCN group. There was no significant difference between the Non-SCN and the Pseudocyst groups. There was no significant difference between the inhomogeneity of the cystic parts, the values were 7.1 ± 0.7, 6.9 ± 0.3 and 7.1 ± 0.6, respectively, in the SCN, Non- SCN and Pseudocyst groups. However, the solid parts' inhomogeneity was significantly higher in the Non-SCN (21.1 ± 0.6; $p < 0.0005$) and in the Pseudocyst (24.3 ± 1.1; $p < 0.0005$) groups than in the SCN (16.1 ± 0.7) group. The calculated value was significantly higher in the Pseudocyst group compared with the Non-SCN group ($p = 0.017$) (Figure 20.*)."* [139]

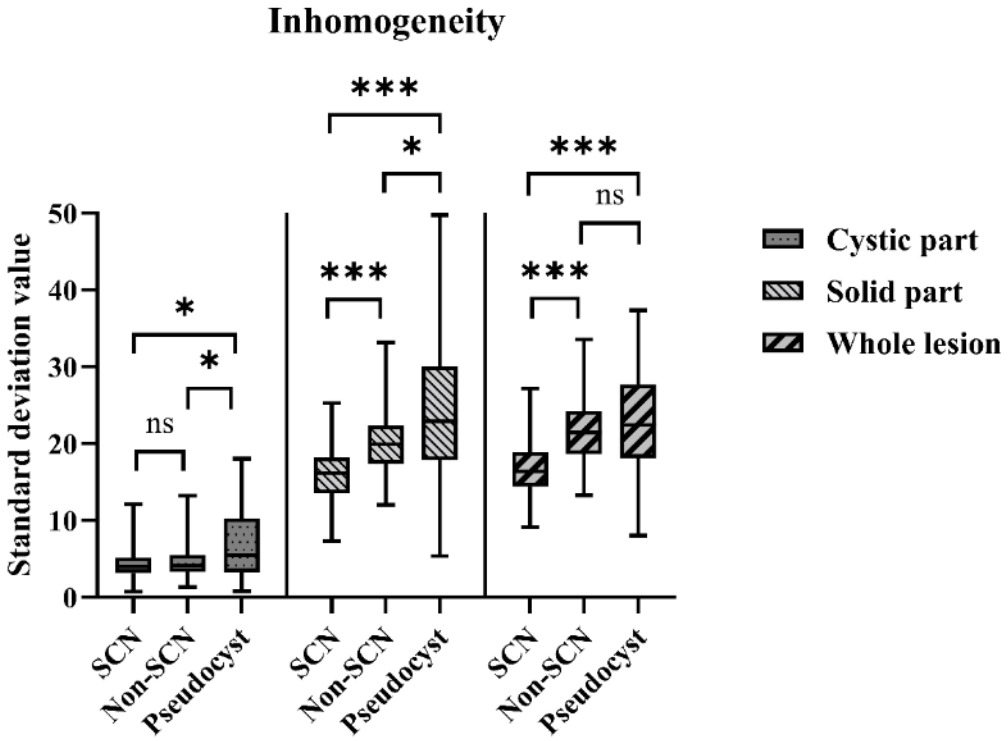

Figure 20. *Inhomogeneity values of the different parts in the groups (without outliner values; *p<0.05, ***p<0.0005, ns=non-significant; the figure was created by the author) [139]*

4.2.5 The density values of cystic lesions and its' parts

"The density of the whole lesions in the SCN, Non-SCN and Pseudocyst groups was 2833.8/mm2 ± 192.6, 4186.6/mm2 ± 135.6 and 2981.6/mm2 ± 144.5, respectively. The density of the Non-SCN group was significantly higher than in the SCN ($p < 0.0005$) and the Pseudocyst ($p < 0.0005$) groups. There was no significant difference between the SCN and the Pseudocyst groups. The density of the cystic parts in the SCN, Non-SCN and Pseudocyst groups was 1461.4/mm2 ± 117.0, 1668.6/mm2 ± 67.57 and 1127.3/mm2 ± 107.1, respectively. In the Pseudocyst group, the density was significantly lower than in the SCN ($p = 0.015$) and in the Non-SCN ($p < 0.0005$) groups. There was no significant difference between the SCN and the Non-SCN groups. The solid parts' density was highest in the Pseudocyst group (6117.9/mm2 ± 25.6), while it was lowest in the SCN group (4737.6/mm2 ± 194.6), meanwhile, in the Non-SCN group it was 5875.0/mm2 ± 183.0. The density of the SCN's solid part was significantly lower than in the Non-SCN ($p = 0.0009$) and the Pseudocyst ($p < 0.005$) groups. There was no significant difference between the Non-SCN and the Pseudocyst groups (Figure 21.)*"* [139]

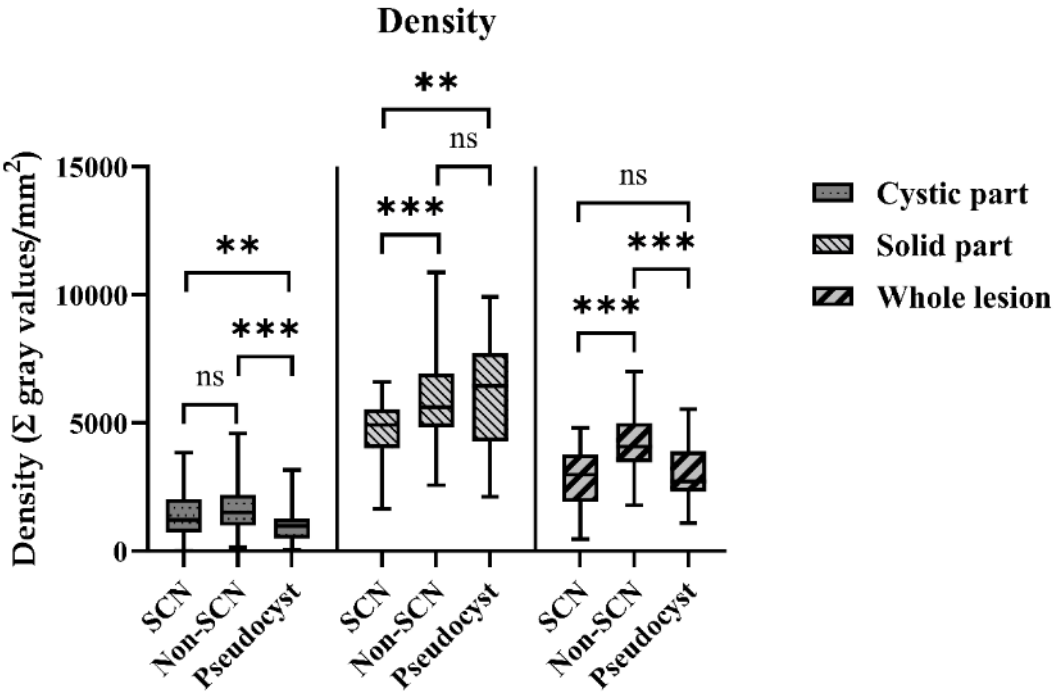

Figure 21. *The density values of the different parts in the groups (without outliner values; **p<0.005, ***p<0.0005, ns=non-significant; the figure was created by the author) [139]*

4.3 Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

4.3.1 Patient demographics and procedure characteristics

"During the study period, 159 patients were initially assessed for eligibility, but only 128 of them (mean age 57.2±11.9 years, 71.9% male) met the inclusion criteria and were included in the analysis; these patients comprised 80 patients treated with a LAMS and 48 treated with a DPPS (Figure 22.). *Patients' baseline and procedural characteristics are summarized in Table 6. Ninety-two patients had a pseudocyst (71.9%) and 36 a WON (28.1%), with the majority of the lesions being located in the body of the pancreas (n=56/128, 43.8%) and transgastric (n=117/128, 91.4%) being the predominant approach. Among the 80 patients treated with LAMS, a stent with a diameter of 15 mm was most frequently used (n=61/80, 76.2%), while among the 48 patients treated with DPPS, stents of 3 cm length (35.2%) and 7 Fr diameter (54.9%) were mainly used."* [140]

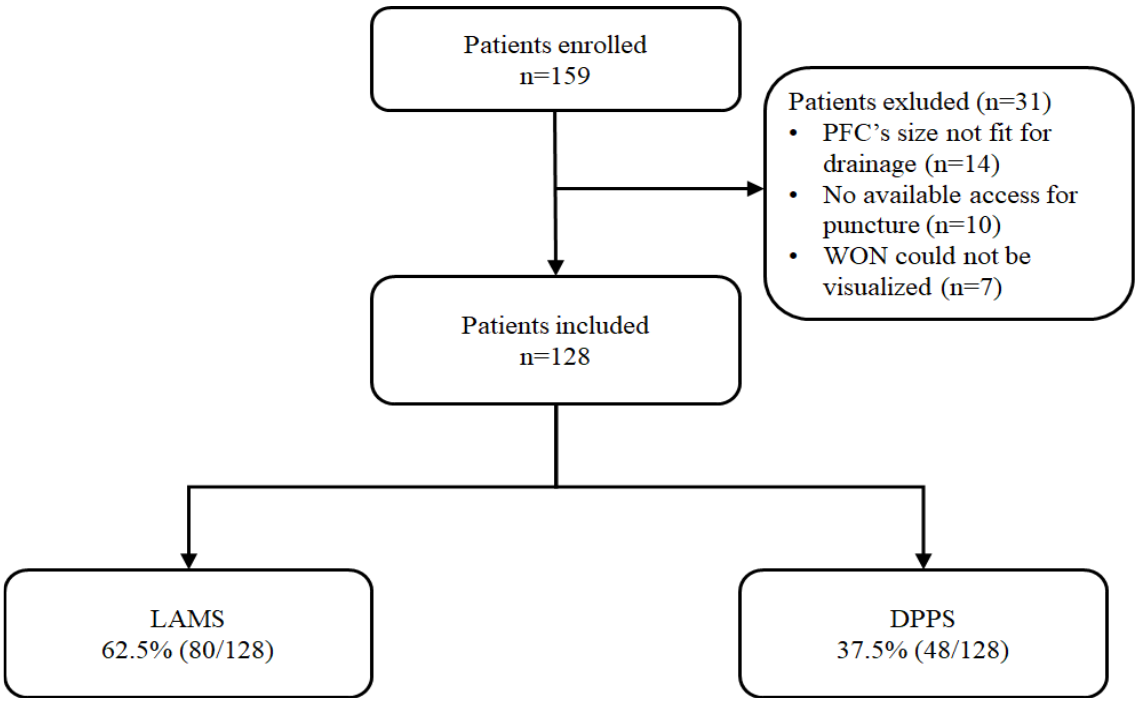

Figure 22. *Research workflow*
A total of 159 patients were enrolled in the study. Out of the 159 patients, 31 were excluded because the PFC was not big enough for drainage, a safe puncture traction could not be visualized, or the WON was not visible at all. Among the remaining patients, 62.5% received LAMS, and 37.5% received DPPS stent. [140]

Table 6. *Patient features and the procedures' technical characteristics [140]*

Characteristics of patients and collections			
Sex & age	WON (n=36)	Pseudocyst (n=92)	Overall (n=128)
Male, n (%)	23 (63.9)	69 (75.0)	92 (71.9)
Female, n (%)	13 (36.1)	23 (25.0)	36 (28.1)
Age (years), mean±standard deviation	60.4±11.3	56.2±12.7	57.2±11.9
Type of PFC, n (%)	WON	Pseudocyst	Overall
	36 (28.1)	92 (71.9)	128 (100)
PFC location, n (%)	WON	Pseudocyst	Overall
Head	2 (5.6)	13 (14.1)	15 (11.7)
Isthmus	4 (11.2)	5 (5.5)	9 (7.0)
Body	16 (44.4)	40 (43.5)	56 (43.8)
Tail	14 (38.8)	34 (36.9)	48 (37.5)
PFC size (cm), mean±standard deviation	WON	Pseudocyst	Overall
	11.8±4.7	11.8±4.7	11.8±4.7
Contributing centers, n (%)	WON	Pseudocyst	Overall
Greece, Athens	16 (44.4)	20 (21.8)	36 (28.2)
Italy, Milan	12 (33.3)	31 (33.6)	43 (33.6)
Croatia, Zagreb	2 (5.6)	17 (18.5)	19 (14.8)
Italy, Foggia/Verona	2 (5.6)	24 (26.1)	26 (20.3)
Hungary, Budapest	4 (11.1)	0 (0)	4 (3.1)
Technical characteristics of transmural drainage			
Drainage access, n (%)	DPPS	LAMS	Overall
Transgastric	46 (95.6)	71 (88.8)	117 (91.4)
Transduodenal	2 (4.4)	9 (11.2)	11 (8.6)
Type of stent, n (%)	WON	Pseudocyst	Overall
AXIOS	28 (77.7)	52 (56.5)	80 (62.5)
Double pigtail	8 (22.3)	40 (43.5)	48 (37.5)
LAMS length (mm), n (%)	WON	Pseudocyst	Overall
10	28 (77.7)	52 (56.5)	80 (100)
LAMS diameter (mm), n (%)	WON	Pseudocyst	Overall
10	6 (21.4)	13 (25.0)	19 (23.8)
15	22 (78.6)	39 (75.0)	61 (76.2)
Number of DPPS, n (%)	WON	Pseudocyst	Overall
1	0 (0)	26 (65.0)	26 (54.1)
2	7 (87.5)	14 (35.0)	21 (43.8)
3	1 (12.5)	0 (0)	1 (0.8)
DPPS length (cm), n (%)	WON	Pseudocyst	Overall
3	4 (25.0)	21 (38.8)	25 (35.2)
4	6 (37.5)	4 (7.1)	10 (14.1)
5	0 (0)	2 (3.4)	2 (2.8)
6	2 (12.5)	15 (27.2)	17 (23.9)
7	2 (12.5)	8 (14.3)	10 (14.1)
8	2 (12.5)	5 (9.2)	7 (9.9)
DPPS size (Fr), n (%)	WON	Pseudocyst	Overall
7	12 (54.5)	27 (50.0)	39 (54.9)
9	0 (43.8)	3 (5.5)	3 (4.2)
10	5 (22.8)	0 (0)	29 (40.9)

4.3.2 Overall primary outcomes

"The overall technical success was 96.9% (n=124/128; 95%CI 93.9-99.9), while clinical success was achieved in 93.0% (n=119/128; 95%CI 88.5-97.4) of the patients. A total of 20 early adverse events were observed, resulting in an adverse event rate of 15.6% (95%CI 9.3-21.9). Overall, there were 4 cases (n=4/128) of initial stent deployment failure; LAMS were used in 3 and DPPS in 1 patient. Regarding LAMS, there was one case of failure to deploy within the cyst, one failure associated with diathermy malfunction and one due to bleeding. The single case of DPPS failure was due to bleeding." (Figure 23.) [140]

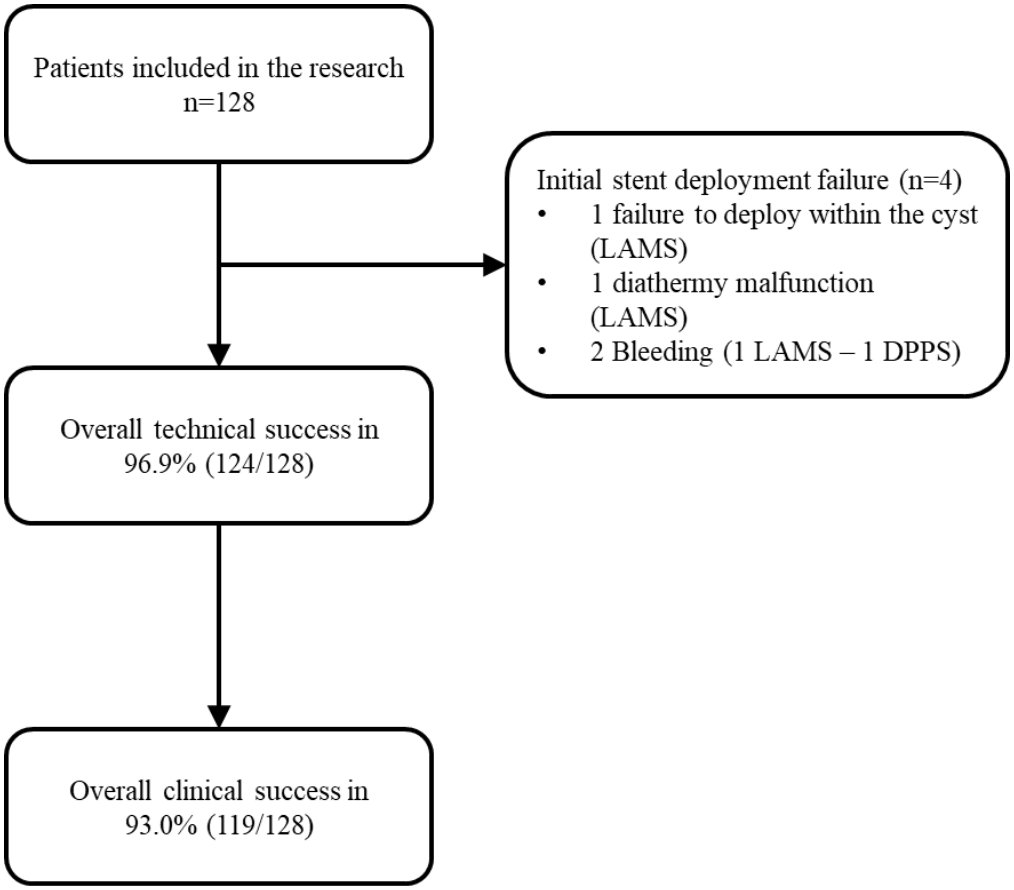

Figure 23. *Technical and clinical success flowchart (The figure was created by the author) [140]*

4.3.3 Secondary outcomes

„Technical success was achieved in 96.3% (n=77/80; 95%CI 92.1-100) of patients in the LAMS group, compared to 97.9% (n=47/48; 95%CI 93.9-100) in the DPPS group (p>0.99). Clinical success did not differ significantly between the LAMS and DPSS groups: 76/80 (95.0%, 95%CI 90.2-99.8) vs. 43/48 (89.6%, 95%CI 80.9-98.2); p=0.29] Drainage time was significantly shorter in the LAMS group (88 vs. 35 days; p<0.001). No significant differences between the 2 groups regarding ease of placement, as rated by endoscopists (6.7 vs. 6.7; p=0.96). The complication rate at stent removal was significantly higher in the LAMS group: 10/80 (13.5%, 95%CI 5.3-19.7) vs. 0/48 (0%, 95%CI 0-0); p=0.03. Tissue overgrowth was the most prevalent complication (n=5/10, 50%), but none of these cases required re-stenting. The mean and median times until LAMS removal were 61.8 and 35 days, respectively." (Figure 24.) [140]

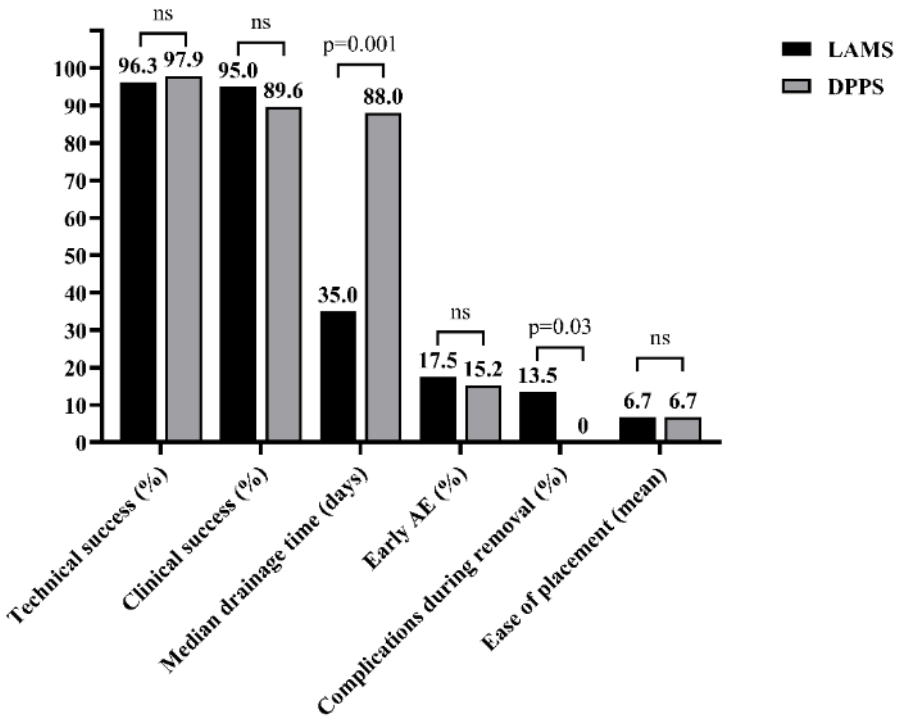

Figure 24. *Assessment of clinical performance in LAMS versus DPPS groups*
There was no difference between the two groups regarding technical and clinical success, early adverse events, and ease of placement. In the LAMS group, drainage time was significantly shorter, but at the same time, the number of complications experienced during the removal of the stent appeared to be higher. [140]

"Technical success was similar for patients undergoing pseudocyst drainage with either a LAMS or DPPS: 51/52 (98.0%, 95%CI 89.7-99.9) vs. 40/40 (100%, 95%CI 91.1-100); p>0.99. The finding was consistent for clinical success and rate of early adverse events: 52/52 (100%, 95%CI 97.1-100) vs. 39/40 (97.5%, 95%CI 86.8-99.9), p=0.435; and 7/52 (13.4%, 95%CI 5.6-25.8) vs. 4/40 (10.0%, 95%CI 27.9-23.7); p=0.750, respectively. Contrariwise, the rate of complications at stent removal was significantly higher in the LAMS group: 8/52 (15.4%, 95%CI 6.8-28.1) vs. 0/40 (0%, 95%CI 0-0); p=0.045. Neither sex nor type of drainage approach (transgastric vs. transduodenal) were found to have any impact on drainage outcomes." [140]

"As far as drainage outcomes among patients with WON is concerned, technical success was similar between LAMS and DPPS: 26/28 (92.8%, 95%CI 76.5-99.1) vs. 7/8 (87.5%, 95%CI 47.3-99.7); p=0.541 (Table 7.)*. Clinical success and rate of early adverse events did not differ significantly between the LAMS and DPSS groups: 24/28 (85.7%, 95%CI 67.3-95.9) vs. 4/8 (50.0%, 95%CI 15.7-84.3), p=0.05; and 7/28 (25.0%, 95%CI 10.7-44.9) vs. 2/8 (25.0%, 95%CI 31.9-65.1), p>0.99, respectively]. The rate of complications at stent removal was also similar between the 2 groups: 2/28 (7.1%, 95%CI 8.8-23.5) vs. 0/8 (0%, 95%CI 0-0); p>0.99."* [140]

Table 7. *Clinical outcomes based on pancreatic fluid collection and stent type [140]*

Pseudocyst, n=92					
Endpoints	LAMS group (n=52)		DPPS group (n=40)		p value
	n (%)	95%CI	n (%)	95%CI	
Technical success	51 (98.0)	89.7-99.9	40 (100)	91.1-100.0	> 0.99
Clinical success	52 (100)	97.1-100.0	39 (97.5)	86.8-99.9	0.435
Early adverse events	7 (13.4)	5.6-25.8	4 (10.0)	27.9-23.7	0.750
Complications at removal	8 (15.4)	6.8-28.1	0 (0)	0-0	0.04
Walled-off necrosis, n=36					
Endpoints	LAMS group (n=28)		DPPS group (n=8)		
	n (%)	95%CI	n (%)	95%CI	p-value
Technical success	26 (92.8)	76.5-99.1	7 (87.5)	47.3-99.7	0.541
Clinical success	24 (85.7)	67.3-95.9	4 (50.0)	15.7-84.3	0.054
Early adverse events	7 (25.0)	10.7-44.9	2 (25.0)	31.9-65.1	> 0.99
Complications at removal	2 (7.1)	8.8-23.5	0 (0)	0-0	> 0.99

4.3.4 Adverse events

„The rate of early adverse events was similar between the 2 groups: 14/80 (17.5%, 95%CI 9.2-25.8) vs. 6/48 (15.2%, 95%CI 3.1-21.9); p=0.61 (Table 8). *Of the severe adverse events among LAMS patients, bleeding was the most common (n=6), with 4 of them eventually requiring angiographic embolization to be controlled. Finally, 2 cases of perforation occurred in each group. In each perforation case, with either LAMS or DPPS, the stent was immediately retracted, and the perforation site was closed with endoscopic clips. The same procedure was repeated with a second cystoenterostomy created successfully at a different location, using LAMS in 2 cases and DPPS in the other 2. It should be noted that the majority of adverse events were effectively managed conservatively, requiring no further surgical intervention."* [140]

Table 8. *Treatment of adverse events and their prevalence [140]*

Parameters	Overall	LAMS group, n=14	DPPS group, n=6	p-value	Pseudocyst n=11	WON n=9	p-value
Adverse event, n (%)				0.157			0.485
Bleeding	7 (35)	6 (42.9)	1 (16.7)		5 (45.6)	2 (22.2)	
Perforation	4 (20)	2 (14.3)	2 (33.3)		2 (18.4)	2 (22.2)	
Migration	3 (15)	2 (14.3)	1 (16.7)		1 (9.0)	2 (22.2)	
Obstruction/fever	4 (20)	4 (28.6)	0 (0)		1 (9.0)	3 (33.4)	
Pain	1 (5)	0 (0)	1 (16.7)		1 (9.0)	0 (0)	
Other (transient pyloric obstruction)	1 (5)	0 (0)	1 (16.7)		1 (9.0)	0 (0)	
Adverse event management, n (%)				0.354			0.642
Conservative*	13 (65)	8 (57.1)	5 (83.3)		8 (72.7)	5 (55.5)	
Additional treatment**	7 (35)	6 (42.9)	1 (16.7)		3 (27.3)	4 (44.5)	

* Administration of proton pump inhibitors, antibiotics, and analgesia
** Stent repositioning or replacement; transarterial embolization in 4 patients due to persistent hemorrhage (all patients had LAMS)

5. DISCUSSION

5.1 Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

The management of patients with suspected choledocholithiasis requires careful consideration, as undiagnosed biliary stones can lead to recurrent symptoms and potentially severe complications (acute pancreatitis, acute cholangitis etc.). However, it is essential not to underestimate the occurrence of rare but possible complications associated with ERCP, such as post-ERCP pancreatitis, bleeding and perforation. Therefore, it is crucial to establish an accurate diagnosis of biliary stones and proper indication for ERCP. [3, 18, 21, 17, 9, 141]

The ASGE 2019 recommendation can be considered a firmer version of the criteria established in 2010, aiming to reduce the number of diagnostic ERCPs because they carry significant risks with only minimal benefits. [25, 27]

According to the guideline, the criteria for the high likelihood group serve as direct indications for ERCP. Based on the guideline from 2010, 42% of our patient population (40 out of 95) would be selected into the high probability group. However, as we have seen, with the 2019 recommendation, this number was reduced to only 25% (24 out of 95). The 2019 guidelines issued by the ESGE, employ even stricter classification of groups to further reduce the number of diagnostic ERCP procedures, thus the exclusive criteria for the high likelihood group are cholangitis or the detection of biliary stones by US. [142]

The positive predictive value of abnormal serum liver enzymes is only 15%, and in the high probability group, there is no significant difference in terms of the assessed laboratory parameters between patients with or without biliary stones. [10] Our study also revealed that laboratory results alone are not suitable for determining the presence of biliary stones. The low specificity and positive predictive value indicate a high number of false-positive cases, thus the specificity of laboratory values concerning biliary stones is unsatisfactory. However, it has been demonstrated that progressively increasing cholestatic serum enzyme levels can serve as predictors of obstruction. [10]

According to some of the published data, US can detect biliary stones in only 15-40% of cases, while in other studies, this value ranges from 22-55%. The sensitivity of US is higher for detecting CBD dilation resulting from choledocholithiasis (77-87%). [4, 10] However, in other studies, the sensitivity for detecting CBD dilation is as low as 46%. [143]

In our study, the sensitivity of US for dilation in cases of choledocholithiasis was found to be 53%. The substantial differences can primarily be attributed to the inherent subjectivity of the examination process. Given the fact, that its diagnostic efficacy is greatly dependent on the examiner's expertise level and patient-specific factors, including obesity and meteorism.

Based on the results of studies, it can be stated that both the negative predictive value of liver function values measured within the normal range and the negative predictive value of US in symptomatic cholelithiasis patients are over 90%. Therefore, if these examinations do not show differences from the normal values, the presence of biliary stones can be likely excluded. [10,26]

The sensitivity and specificity of certain elements that was established by ASGE are suboptimal. Elevated serum laboratory parameters were observed in the majority of patients suspected of biliary stones, and a significant percentage of them also exhibited biliary dilation. In our study, the confirmed presence of biliary stones in the high and intermediate likelihood groups determined by ASGE predictors was 63% and 55%, respectively. These values are far from the remarkable diagnostic sensitivity of EUS (98%). [9]

EUS is a more invasive imaging modality compared to the tests on which the predictors are based. However, it is incomparably more accurate in confirming choledocholithiasis, furthermore its application allows for the detection of alternative biliary abnormalities. Moreover, EUS does not only aid to establish the indication for ERCP but also helps avoiding additional, unnecessary endoscopic interventions that carry a risk of significant complications. This, in turn, reduces the rate of complications and associated costs. [21,17,9,30]

According to an international study, even in the high probability group, ERCP can be avoided in 57.7% of cases. Therefore, it is advisable to consider performing EUS before ERCP. [19] According to other prospective studies, EUS is a valuable diagnostic

tool for the evaluation of suspected biliary stones because of its high diagnostic value. [9,28,29]

5.2 Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

There are many benefits of using EUS as an imaging modality, such as the ability to see organ walls in detailed structures and how they correspond to their histological layers. In addition, it also has a high diagnostic yield when analyzing nearby structures and has the ability to perform real-time guided tissue acquisition (FNA or FNB). EUS can detect the small pancreatic lesions with the greatest sensitivity, however, the method is semi-invasive, highly operator- and skill dependent, and requires a significant learning curve to become proficient.

The practitioner's expertise level significantly affects the efficiency of the EUS examination, and consequently the clinical outcome of the patient. It is difficult to distinguish between cystic lesions based solely on their EUS appearance, benign, malignant, or even inflammatory lesions may appear to be the same.

The precision of diagnosis can be enhanced by EUS-guided sampling (FNA or FNB). In solid pancreatic neoplasms, recent studies have demonstrated that EUS-FNA has 91% sensitivity and 94% specificity. However, in cystic pancreatic neoplasms, the test exhibits worse, with sensitivity and specificity of 54% and 93%, respectively. For optimal diagnostic efficiency, the combination of EUS morphology, EUS-guided tissue sampling’s patho-cytological analysis, and the assessment of intracystic CEA level is required. [144-150]

Novel remarkable advancements in the field of software development offer excellent opportunities to support decision-making based on actual quantitative facts and data rather than skill-dependent and subjective predictions to achieve accurate results.[148]. The emerging use of digital image processing in healthcare is opening new horizons to optimize the efficiency of diagnostic performance across the field. [151] By defining the appearance of the lesions using quantitative data, the software processing of EUS images may help to assess cystic lesions of the pancreas and assist in the decision-making process.

In our study the gender ratio did not significantly differ across the groups, even though most patients in the SCN and Non-SCN groups were female, while the Pseudocyst group had a lower proportion of female patients. These demographic findings correlate with previous observations. [152] There was also no marked variation in the age distribution.

The evaluation of the overall lesion's size revealed no statistically significant difference, despite the slightly larger pseudocysts. Since the majority of our enrolled cystic lesions were accidentally found previously using various imaging techniques, thus their etiology was unknown. The known and followed Pseudocysts were excluded from the study, as EUS was not performed for follow-up due to their known etiology; particularly, Pseudocyst with enormous size were not enrolled.

The majority of SCN lesions with typical morphology and characteristics (elderly female patient, central calcification, spongy mass, microsyctic appearance) that were diagnosed by CT or MRI (even incidentally) were not assessed by EUS but were followed-up with cross-sectional imaging. Therefore, due to the observational nature of our study these cases were not enrolled. To further evaluate the SCNs showing a non-typical morphology, an EUS examination was performed, these SCNs were either unilocular or oligocystic. Because the cystic regions of the microcystic-type SCNs lesion are sometimes too small to be visualized even on the EUS, these lesions may be recognized as solid lesions. Currently, most of the indications for pancreatic resections are based primarily on the lesions' size, however studies have shown that a substantial number of invasive MCNs are smaller than 4 cm, which highlights the need for a stricter follow-up strategy with objectively measurable morphology features in addition to the lesions' size. [153]

SCN and Non-SCN lesions predominantly had more than two large cystic lobules, pseudocyst lesions typically had just one. In contrast to the pseudocyst group, there was no significant difference in the quantity of cystic lobules between the SCN and Non-SCN groups. Since microcystic SCN lesions with a typical characteristic structure are often detected by MRI or CT and are thought to have more cystic lobules, further EUS evaluation is not essential. Even an experienced eye can be fooled by oligocystic, unilocular, or microcystic SCNs with unusual shape, since around 30% of SCN lesions have a non-classical appearance. This can result in an astonishing number of needless

operations. Since pancreatic resection may be associated with severe complications, as well as perioperative morbidity, and mortality, it is not indicated in all patients with pancreatic cystic lesions. [154] Taking into consideration the principles of the step-up approach and cost-benefit risk assessment, it is preferable to follow up the majority of cystic lesions. The differential diagnosis between the atypical SCN and MCN is far more challenging than the conventional SCN and MCN distinction in pre-operative diagnostics. [154]. In the pseudocyst group, the fraction of cystic part(s) to the overall lesion was highest. The Non-SCNs usually had a higher number of cystic portions, but the cysts were smaller, meaning that their area ratio was the lowest.

The gray mean values of the lesions were used to measure the lesions' echogenicity. The overall lesion echogenicity was the most prominent in the Non-SCN group and corresponded with the area ratio. The total of measured gray mean values for the entire lesion increased with the proportion of solid areas in the whole lesion. Since pseudocysts typically present with thick and hyperechogenic cystic walls—a feature that can be explained by their fibrotic cyst wall histology—the gray value of the solid parts was greatest in the pseudocyst group. The SCN lesions had the lowest value as they are exclusively defined by the epithelium, whereas the solid portions of the Non-SCN lesions are even less echogenic. This was mostly because the MCN lesions' mucin-producing epithelium is usually supported by ovarian-type stroma. [154]

In conclusion, the sizes of the cystic portions differed widely, but not the overall lesion size. The currently available guidelines do not take into account the lesion's area ratio; instead, they solely rely on the size of the lesion as a whole (pseudocysts mostly have only cyst wall while MCNs have more solid parts). It is also problematic to interpret other worrisome features, including thicker or enhanced cyst walls, because these characteristics are neither measured nor standardized in the guidelines. In our study it was revealed that the interpretation of the gray values of the different lesion parts and the different worrisome features are easily quantifiable, and the considerable differences should be taken into consideration when making therapeutic decisions. [31]

The sensitivity and diagnostic accuracy of EUS can be augmented by supplementing its diagnostic value with easily quantified, objective variables that are invisible to the human eye. Enhancing pre-operative diagnostic accuracy can also lead to

fewer unnecessary procedures and interventions, which can optimize the clinical outcome by facilitating more accurate and economical the decision-making. [145, 146].

5.3 Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

Over the past decades, EUS-guided transmural drainage has transformed the treatment of symptomatic PFCs by encouraging the use of a minimally invasive intervention that has achieved in technical success rates exceeding 90% and clinical success rates ranging from 75% to 90%. [155, 156]. Furthermore, the introduction of LAMS held the potential of solving the underlying limitations of DPPS. [99] However, there is currently insufficient data in the published literature to support the use of LAMS rather than DPPS in resolving PFCs. Therefore, the guidelines recommend using LAMS or plastic stents for endoscopic transmural drainage [157]. Since data on the effectiveness of LAMS are still insufficient, we must admit that this is just a mild recommendation based on moderate quality of evidence.

The primary endpoint assessment of our study indicated positive outcomes and an exceptional patient safety profile, in addition to excellent rates of technical and clinical success (97% and 93%, respectively). The endoscopy assisted transmural PFC draining might be difficult. [99] Biliary DPPS placement has been shown to be an effective treatment for symptomatic PFCs based on initial data. [158] However, subsequent studies have revealed drawbacks such as the need for multiple stenting to ensure sufficient drainage due to the narrow stent luminal diameter, obstruction and superinfection and worse outcome when applied in case of WON, stent-related adverse events up to 18%, and technical challenge in placing multiple DPPS. [97] These insights led to the development of LAMS. The large lumen of LAMS makes possible a more feasible endoscopic necrosectomy and better drainage. The bilateral rims allow tight tissue binding, reducing the probability of migration. [99] Further than their theoretical benefits, evidence showed that these devices were truly effective, with a 95% of technical success rate and 85%–90% of clinical success rate, with a 5% of migration risk. [118, 121, 159]

Besides the most available published data, our study also showed that LAMSs have a technical and clinical success rate comparable to DPPS in the treatment of PFCs. Although LAMSs have been used more recently for endoscopic drainage of PFCs, there

are still few large prospective studies comparing their clinical or technical success to DPPS. As a result, choosing between stents depends on several factors, including the endoscopist's judgment, local preference and expertise, reimbursement policy, instead of definitive evidence that prioritizes one type of stent over another [157]. There was no substantial difference in treatment response comparing LAMS and plastic stents in one randomized controlled study that is currently available [160]. Numerous meta-analyses have focused on this topic as well; the most recent and comprehensive of them found no noticeable difference in technical success or adverse events between LAMS and DPPS. While the use of LAMS was related with greater clinical success, decreased recurrence, and required fewer follow-up procedures, however it is important to highlight that the use of LAMS was linked to more perforations in WON trials. [156] A thorough look suggests that even these findings need to be interpreted carefully. Particularly since most of the individual studies that were included had a retrospective methodology, included various metal stent types, or evaluated the efficiency of LAMS or DPPS independently, thus there are concerns about these studies' heterogeneity and prejudice. [155] Future randomized controlled trials with sufficient power should methodically assess variables (such as the type of lesion, its location, and the level of skill of the endoscopist) that may enable the discovery of treatment effect heterogeneity and finally resolve this disagreement.

The discovery that LAMS deployment had a greater adverse event rate in comparison to DPPS is an important observation that warrants further consideration. This incidence is consistent with the findings of the most comprehensive and latest meta-analyses in this subject. [155, 161] Furthermore, regarding of PFC drainage, bleeding is the most concerning adverse event associated with LAMS, also based on the data of our study. Individual studies and meta-analyses also support the finding that the bleeding risk is higher in the cases of LAMS compared with DPPS (19% vs. 1%; p=0.003). This can be explained by the potential fact that the radial tension applied by the LAMS to the cyst walls may help to stop the bleeding, but bleeding risk still exists since the stent may erode the posterior cavity wall if the cavity collapses after drainage. Although this hypothesis was not confirmed by other major registry-based investigations. [162, 163, 164] This might be because WON was the only type of lesions included, or it could be due to a combination of PFCs, variations in the endoscopist's skill level, and discrepancies in how adverse events are defined and interpreted.

Encapsulated necrotic materials are hardly reabsorb spontaneously, in fact, 60% of cases require endoscopic necrosectomy. LAMS appear to perform better than the other alternative methods in the therapy of WON. [99, 165] However, there's a few published information about the drainage of pseudocyst. [166] Despite the differences in the outcomes after endoscopic intervention, available studies typically include pancreatic pseudocysts and WON together in their analysis, complicating this issue. Regarding the procedural results of WON and pseudocyst drainage, our study showed comparable performance between the DPPS and LAMS groups; the only difference was that the LAMS group experienced a greater rate of complications following removal.

When it comes to the implications for clinical practice, the PFC's unique characteristics undoubtedly play a crucial role in determining which stent is best for the particular situation. Therefore, LAMS appears to be the best option for WON drainage; however, multiple DDPS emplacement is the preferred option for the primary clinical management for patients with pseudocysts, as this approach is not only more cost-effective [100], but also more reliable and safer over the long term, as demonstrated lately. [167] However, much remains to analyze and work on [168], since variables including patient compliance, integrity of the pancreatic duct, clinical condition, and endoscopist's skill level are examples of "gray" regions where possible influence on the effectiveness of each approach is not yet understood.

Our study's multicenter design is perhaps one of the main strengths, which faithfully mirrors the everyday real-world clinical management and greatly enhances the representativeness of the sample. Other advantages of the study include the high number of patients recruited the application of standard definitions for adverse events, and the implementation of strict diagnostic criteria.

We also need to address some of the limitations of our study, the most significant is its retrospective design. Investigating the collective experience of a fairly great cohort from 10 tertiary medical centers across Europe, enriches the international literature by providing not only actual information throughout a continent, but also support the real-world evidence that is more and more essential for healthcare decisions. One might reject the quality of the evidence provided, given its relation to the previous publications on the topic. Besides randomized controlled trials, larger observational studies that accurately show the routine clinical practice can also produce real-world evidence. From this

perspective, the current research represents a type of innovation that might broaden our understanding to aid the decision-making, enhancing safety and efficacy, and eventually patient-related results. It is essential to clarify that this research was limited to a particular commercially available LAMS design, making it impossible to draw generalizations to other LAMS. Also, variances in doctors' performance and clinical circumstances may have contributed to heterogeneity because the stent management strategy and follow-up protocol were neither consistent nor standardized between locations. Another drawback is that each physician's evaluation was utilized to choose which kind of stent (DPPS or LAMS) to deploy. Finally, we did not do an official cost-effectiveness analysis, report on the number of necrosectomy sessions, their success, or the PFC recurrence rate following stent removal, nor did we investigate late adverse events.

6. CONCLUSION

6.1 Diagnostic sensitivity of endoscopic ultrasound in patients with suspected choledocholithiasis

- EUS showed a diagnostic sensitivity of 98% and a specificity of 100% in cases of suspected choledocholithiasis. These results indicate that EUS is a highly sensitive and accurate diagnostic tool for the detection and evaluation of common bile duct stones. EUS can help avoiding unnecessary invasive procedures like ERCP and reducing the risk of complications associated with it.

- The diagnostic accuracy of the ASGE guideline was evaluated in our study. The sensitivity and specificity of the guideline in predicting choledocholithiasis was found to be moderate and not satisfactory. The predictor factors defined by the ASGE guideline, were used to stratify patients into low, intermediate, and high likelihood groups of choledocholithiasis. These predictor factors alone were not sufficient to accurately predict the presence of common bile duct stones.

- The limitation of our study is a small sample size, operator dependent factor of the EUS (highly skill dependent) and 2-month follow-up period which for some cases may not be sufficient to capture all potential outcomes related to choledocholithiasis.

6.2 Quantitative software analysis of endoscopic ultrasound images of pancreatic cystic lesions

- Our study found significant differences in echogenicity, area ratio, gray values, and density among the different types of lesions. The significant differences highlight the potential of EUS image analysis as a diagnostic tool for evaluating and distinguishing pancreatic cystic lesions.

- Further research and validation are recommended to assess the clinical efficacy and accuracy of this method in clinical practice. The clinical implications of the method could be supplementary to other diagnostic procedures.

- The limitation of the study is the limited number of images, operator dependent diagnostic method (EUS) and rudimentary software image analysis method.

6.3 Efficacy and safety of endoscopic drainage of peripancreatic fluid collections: a retrospective multicenter European study

- The technical success rates were similar for patients undergoing drainage with LAMS and DPPS, with high rates of technical success achieved in both groups.

- When comparing the clinical outcomes and adverse events between drainage with LAMS and DPPS, both modalities achieved equal rates of technical and clinical success. Although, there were differences in adverse events, with a higher incidence of early adverse events observed in cases where LAMS were used compared to DPPS. The most common adverse event related to LAMS was bleeding, whereas complications at stent removal were also more prevalent in the LAMS group. The median drainage time with LAMS appeared to be less.

- The main limitation of the study is its retrospective design. The study also did not undertake an official cost-effectiveness analysis, report on late adverse events, or the number of necrosectomy sessions. Additionally, the decision which type of stent to use was based on each physician's assessment, leading to variability among physicians and clinical settings, which could result in heterogeneity in the outcomes.

7. SUMMARY

The EUS is a highly sensitive and accurate diagnostic tool for detecting and evaluating choledocholithiasis, even in cases where the previous US examination did not confirm the presence of biliary tract stones. The sensitivity of clinical predictors for estimating biliary tract stones are far from satisfactory. The possible predictive ability of clinical parameters determined by the modified 2019 (or the 2010) ASGE guideline for the detection of choledocholithiasis could not be proved in our study.

The EUS-guided drainage of PFCs demonstrates a high level of technical and clinical success, regardless of the choice between LAMS or DPPS. While the incidence of early complications was comparable for both stent types, it is noteworthy that there was a slightly higher incidence in the LAMS group, although this difference did not reach statistical significance. Nevertheless, it is also essential to highlight, that the drainage duration required for PFCs was significantly lower in the LAMS cohort.

During the analysis of EUS images of pancreatic cystic lesions, there was no significant difference in the overall lesion size; however, significant differences were found in the dimensions of the cystic components. The presently existing guidelines solely rely on the overall lesion size and do not account for the differentiation based on the lesion's area ratio. Pseudocysts typically feature predominantly cyst walls, while MCNs exhibit a higher proportion of solid components. Furthermore, concerning features like thickened or enhancing cyst walls lack quantification and standardization in the guidelines, which makes their interpretation challenging. In our study, we quantified the echogenicity of distinct lesion components, and the considerable variances in these parameters may offer valuable insights for guiding clinical decision-making processes. Nonetheless, further scientific investigation is warranted to validate these findings. The software analysis of EUS images may hold promise as a novel diagnostic tool for assessing and distinguishing pancreatic cystic lesions. Moreover, it could expand the role of artificial intelligence in the diagnosis of gastrointestinal disorders. However, further comprehensive research is recommended to validate the clinical effectiveness and precision of the EUS image analysis methods.

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