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Endoscopic Ultrasound in Pancreatology: Focus on Inflammatory Diseases and Interventions

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Abstract
Background: Endoscopic ultrasound (EUS) is a main tool in pancreatology for both diagnosis and therapy. It allows minimally invasive differentiation of various diseases, with a minimal degree of inflammation or anatomic variations. EUS also enables interventional direct access to the pancreatic parenchyma and the retroperitoneal space, the pancreatic duct, the pancreatic masses, cysts, vascular structures for diagnostic and therapeutic purposes. ***Summary:*** This review aimed to summarize the new developments of EUS in the field of pancreatology, with special interest on inflammation and interventions. EUS enables way to perform pseudocyst drainage, necrosectomy, transenteral drainage and transenteric access of the main pancreatic duct, or the direct visualization or therapy of vascular structures adjacent to the pancreas. ***Key Messages:*** EUS has a deep impact on pancreatology, and the development of new diagnostic and interventional approaches to the retroperitoneal space and the pancreas has increased in the last years exponentially, allowing minimal invasive diagnostics and therapy and avoiding surgery and percutaneous therapy.

Introduction

Endoscopic ultrasound (EUS) is a fundamental tool for diagnosis and therapeutic procedures in gastroenterology, hepatology, and pancreatology. It combines the profits of endoscopy to gain access to human cavities with the features of high-frequency ultrasound probes to achieve superior visualization of anatomical regions, making pinpoint diagnostics possible. The aim of this review is to summarize the most important indications and recent development of diagnostic and therapeutic EUS for the management of inflammatory diseases of the pancreas and to highlight its most recent advancements and perspectives.

EUS for the Diagnosis of Acute Pancreatitis

EUS is a milestone diagnostic tool in the diagnosis of biliary etiology of acute pancreatitis. The high resolution of EUS (0.1 mm) accounts for its particular sensitivity to biliary stones smaller than 5 mm or microlithiasis, regardless of the bile duct diameter [1]. For biliary sludge detection, interobserver agreement among endosonographers is only moderate [2]. If stones are detected, ERCP can also be carried out in the same endoscopic session without any further sedation. One prospective RCT [3] showed no significant superiority of EUS over MRCP in diagnosing biliary disease in patients with

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intermediate risk of choledocholithiasis (i.e., patients with dilated CBD on ultrasound of the abdomen and/or altered LFTs). On the other hand, both a Japanese RCT conducted in patients with suspected common bile duct stones but negative computed tomography [4] and a recently published meta-analysis showed higher sensitivity and accuracy of EUS over MRCP in detecting choledocholithiasis [5]. In one prospective study in patients with idiopathic acute pancreatitis [6], EUS found more biliary stones, whereas MRCP identified pancreatic duct abnormalities with higher sensitivity. Ortega et al. [7] demonstrated that EUS was significantly more likely to detect gallbladder disease and chronic pancreatitis than MRCP.

EUS is also important for the workup of idiopathic acute pancreatitis [8]. Any obstruction of the pancreatic duct can cause acute pancreatitis, so in cases of unclear etiology, pancreatic adenocarcinoma, metastases, intraductal papillary mucinous tumors, or neuroendocrine tumors should be ruled out after the acute inflammatory changes are resolved, as suggested by European and American guidelines [9, 10]. If the patients are older than 40 years, the risk of diagnosing pancreatic cancer after an episode of idiopathic acute pancreatitis is increased compared to the overall population [11].

In one prospective study comparing ERCP, secretin-enhanced MRCP, and EUS in acute recurrent pancreatitis, EUS was able to find the underlying pathology in 79.5% of patients. Herein, EUS most commonly reported pancreatic ductal changes such as main duct or side branch dilation in 38.6% of cases and biliary disease or cysts <3 mm in 18.2% of patients [12]. These results were confirmed in a study conducting EUS in patients with a first attack of idiopathic pancreatitis, where a cause was identified in about 80% [13].

EUS and MRCP should both be used in the diagnostic workup of idiopathic acute pancreatitis as complementary techniques and follow-up examinations are suggested in order to rule out a neoplasm as a cause of obstructive pancreatitis or an early onset of chronic pancreatitis [14]. Several studies have been done to find predictor factors for severe pancreatitis [15, 16].

EUS is not performed routinely to predict the severity of acute pancreatitis; however, a study showed that diffuse parenchymal edema, periparenchymal fluid collections, diffuse retroperitoneal fluid accumulation, and peripancreatic edema are more common in severe acute pancreatitis [15]. Cho et al. [16] found a geographic hyperechoic area during acute pancreatitis – a pattern characterized by background hypoechogenicity with focal interspersed strongly hyperechoic areas – as a possible histologic correlation with a reversible early focal parenchymal change attributed to a spotty severe inflammatory area with hemorrhage surrounded by edema. Such hyperechoic changes were found in the early phase of acute pancreatitis, are associated with a worse outcome, and are reversible under therapy.

Complications of Acute Pancreatitis: Treatment of Pancreatic Fluid Collections and Disconnected Pancreatic Duct Syndrome

Pancreatic fluid collections develop in 30–60% of patients with acute pancreatitis, and pseudocysts represent 5–15% of cases. More than 80% of these cases show a spontaneous resolution or decrease in size over time [17]. Generally, asymptomatic pancreatic pseudocysts less than 5 cm in diameter are known to resolve spontaneously [18]. If pseudocysts do not resolve and the patients show symptoms, EUS-guided drainage is needed. Approximately 10–20% of patients develop severe acute pancreatitis and pancreatic necrosis [19]. After approximately 4 weeks, necrosis gets walled off leading to the formation of walled-off necrosis (WON) [20]. The natural course of necrosis can be different: the majority (about two-thirds) of sterile pancreatic necroses – regardless of size – resolve spontaneously [21]. If a total resolution does not occur, they may become symptomatic – usually with pain, mechanical obstruction, or fever. The most dangerous complication of pancreatic necrosis is superinfection, which is associated with a high mortality [19] and complications after drainage therapy [22]. In these cases, drainage therapy is indicated. In the treatment of WON, well-established approaches have been developed: endoscopic, percutaneous, or surgical therapy. In the last 20 years, management of pancreatic necrosis has shifted away from aggressive open necrosectomy to less invasive approaches through natural cavities, i.e., endoscopic approaches. The endoscopic approach, which was first described by Baron et al. [23] in 1996, allows access to the necrotic cavity by puncturing the wall of the gastrointestinal tract. Before the introduction of large lumen metal stents, only plastic stents and irrigation of the necrotic collection with a nasocystic drainage were the standard of care. To optimize the drainage of necrotic collections and allow direct access to the retroperitoneum to perform endoscopic necrosectomy, lumen-apposing metal stents (LAMS) were developed [24, 25]. Since then, many trials had been addressed to compare plastic stent to metal stents. Despite enthusiasms for the newly introduced metal stent, lastly published trial showed that double-pigtail plastic stents were not inferior to LAMS [26] (Fig. 1). These results were confirmed by data from the prospective multicentric study of Boxhoorn et al. [27], which showed that the need for endoscopic transluminal necrosectomy in patients with infected necrotizing pancreatitis treated with LAMS was not lower compared to plastic stents [27, 28]. A combination of the two stent may be a novel strategy for the treatment of pancreatic necrosis. Indeed, a recent RCT from Vanek et al. [29] showed how anchoring coaxial

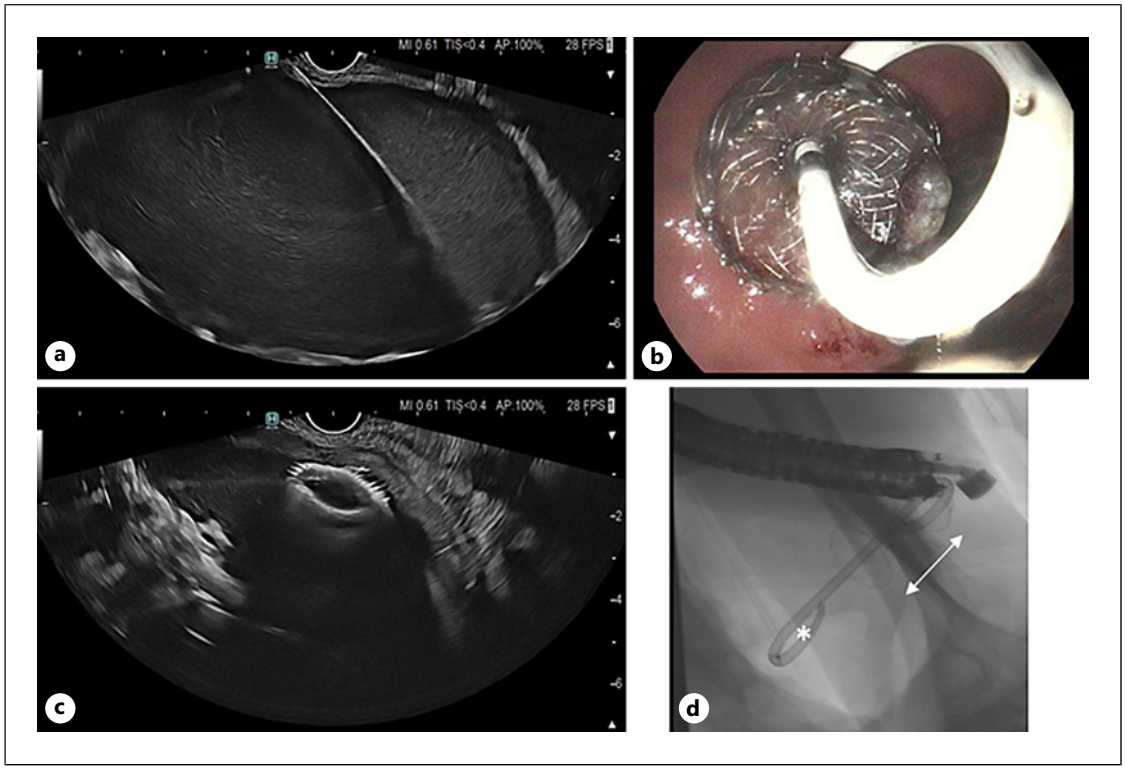

Fig. 1. Endoscopic (**b**) and EUS (**c**) views of a lumen-apposing metal stent (LAMS) draining the infected necrosis. **a** FNA puncture of an infected walled-off pancreatic necrosis with placement of a guidewire. **d** Fluoroscopy of the LAMS (double-headed arrow) with indwelling double pigtail stent (*).

double-pigtail plastic stents within LAMS reduced both stent occlusion rate and advert events by reducing luminal trauma. Which type of stents should be chosen is still a matter of debate, as, on the other hand, one recent trial indicated that LAMS could reduce the inflammatory response, the new onset of organ failure, and the hospital stay compared to plastic stents [30]. According to results from the EUS interventional group of Orlando, LAMS could be the appropriate treatment for patients presenting with pancreatic fluid collections containing more than one-third of necrosis and systemic inflammatory response syndrome as well as patients requiring intensive care [30]. Although previous studies demonstrated that the ideal time for the drainage of WOPN is after 4 weeks, newer studies showed that similar technical and clinical outcomes were also achieved for earlier drainage [31]. On the other hand, regarding the duration of treatment, the previous time threshold with a maximum of 4 weeks for indwelling LAMS [32] was recently questioned in two large retrospective studies [33], pointing out the need for future studies to establish the optimal time for LAMS removal.

In order to avoid recurrences of fluid collection and long-term complications like parenchymal atrophy, clinicians have to be aware of the disconnected pancreatic duct syndrome, which occurs in 20–40% of patients with severe acute pancreatitis [21]. The necrosis of the pancreatic parenchyma may affect the main pancreatic duct with a discontinuity between the left-sided pancreas and the duodenum. Such discontinuation creates a permanent leak, which gives rise to the disconnected pancreatic duct syndrome [34]. Patients with partial or complete pancreatic duct interruption have a higher incidence of recurrent or refractory fluid collections or recurrence of pancreatitis [35]. Diagnosis is made by imaging. One prospective study reported on the ability of EUS in detecting the pancreas duct disruption with consecutive disconnected pancreatic duct syndrome. In this study, EUS could make the diagnosis correctly in all of the patients included (n = 21), if the pancreatic duct could be visualized sufficiently, which is not always possible [36]. EUS can also be used to perform an EUS-guided pancreatogram. The correct diagnosis of a disconnected pancreatic duct has an important clinical implication in the choice of the EUS drainage approach. In these cases, a double-pigtail plastic stenting may be more appropriate than LAMS in order to allow for long-term drainage of the fluid collection by creating a fistula between the lumen and the disrupted pancreatic duct. A short-term drainage of the collection with LAMS may favor the early recurrence of the pancreatic fluid collection [37–39].

Pancreatic fluid collections in the context of disconnected pancreatic duct can present as pseudocysts or peripancreatic fluid collections. In case of walled-off pancreatic necrosis associated with a disconnected

pancreatic duct, LAMS are usually the therapy of choice since interventions like repeated necrosectomy are easier to perform due to their larger diameter [19]. However, since LAMS have been associated with increased adverse effects when left in situ for more than 4 weeks [40] and long-term double-pigtail drainage has been demonstrated to lower rates of peripancreatic collection recurrence, LAMS should be replaced with double-pigtail stents if pancreatic duct rupture is suspected [39]. Long-term efficacy and safety have been demonstrated for double-pigtail stents in cases of disconnected pancreatic duct from retrospective studies, even if the stents were occluded in the further course [41, 42]. This is possible because the pancreatic fluid can pass along the stent through the fistula in the gastrointestinal tract. However, one quarter of the collections will recur, particularly in cases of complete rupture of the pancreatic duct, chronic pancreatitis, in case of stent migration or a long stent (>6 cm) depicting a long fistulous tract, as multivariate analyses of one study have shown [43].

One prospective study demonstrated that half of the recurrences of fluid collections in patients with a disconnected pancreatic duct were asymptomatic and did not require re-intervention [44]. Moreover, a recent RCT did not prove the efficacy of plastic stent over no-stenting after removal of LAMS in the reduction of recurrence of fluid collections [45]. On the other hand, the drainage of the upstream disconnected segment of the pancreatic duct may prevent pancreatic atrophy and the onset of pancreatogenic diabetes [44]. In brief, there remains a role for plastic stents in the management of complications of acute pancreatitis, particularly in patients with pseudocysts and in the setting of disconnected pancreatic duct syndrome.

EUS for the Treatment of Vascular Complications of Acute Pancreatitis

Vascular complications of acute pancreatitis are rare with a reported incidence of 5% but can be life-threatening and sometimes difficult to diagnose in clinical practice [46]. The vascular complications are splenic artery pseudoaneurysm and thrombosis of the splenic vein or peripancreatic branches of the portal system, with development of left-sided portal hypertension. Bleeding from gastric varices due to left sided portal hypertension or ectopic varices can be easily localized and treated (in experienced hands) with EUS-guided coil and glue injection [47].

Pseudoaneurysm can rupture and bleed into the peritoneum, presenting clinically as tender abdomen with an increase in ascites. Bleeding from splenic artery aneurysm, which is sometimes caused by peripancreatic fluid drainage [48], can be treated with radiological intervention. Alternatively, an increasing number of case series describe the injection of sclerosing glue or coils directly under EUS guidance, where endoscopic view is completely hampered by bleeding [46, 49, 50].

EUS for the Diagnosis of Chronic Pancreatitis

Pancreatic function tests for diagnosis of chronic pancreatitis are cumbersome for patients and have very limited availability [51], whereas other imaging techniques mostly pick up advanced morphological changes. EUS is considered to be the most sensitive imaging modality to diagnose chronic pancreatitis [52–54] because it can detect early fibrotic alterations of the pancreas. In prospective studies, both radial and linear endosonographic transducers have been shown to be equally accurate for the diagnosis of CP [55]. Early changes that are visualized in EUS both in pancreatic parenchyma and the ductal system are not always associated with clinically relevant disease [56], so several diagnostic criteria have been developed: Cambridge Classification [57], Wiersema classification [58, 59], Milwaukee criteria, or Rosemont classification [60, 61]. Nine criteria (5 changes in the ductal system and 4 changes in the pancreatic parenchyma) have been introduced by Wiersema et al. [58, 59]. All the new classification systems are based on such criteria, whereas further classifications added more criteria, as in the Rosemont classification. In this classification, Catalano et al. [62] added two more criteria: structural inhomogeneity and lobulation without honeycombing (non-contiguous lobules). In this last classification, a combination of major and minor criteria is evaluated to weight the structural changes. In every classification, a cut-off of less than two criteria is used to rule out clinically significant chronic pancreatitis [63]. Increasing the number of EUS criteria required for diagnosis increases specificity; lowering the threshold number of criteria increases sensitivity but decreases the already poor specificity of EUS [62, 64].

Conventional EUS criteria for diagnosis of CP rely on the evaluation of nine features. The four parenchymal features include hyperechoic foci (distinct 1–2 mm hyperechoic points), which correlate histologically with calcifications, hyperechoic strands (hyperechoic irregular lines >3 mm), lobularity (2–5 mm lobules), and cysts (thin-walled hypo/anechoic structures >2 mm within the parenchyma). Five ductal features include MPD dilation (>3 mm in the head, >2 mm in the body, and >1 mm in the tail of the pancreas), ductal irregularity, hyperechoic duct margins, visible side branches, and intraductal stones (intraductal echogenic structures with acoustic shadowing) [65]. The ideal cut-off for the number of EUS criteria needed to diagnose CP varies in the literature. In a

study assessing conventional EUS criteria in patients who underwent pancreatic surgery, the presence of ≥4 criteria was the best predictor of histological CP with sensitivity, specificity, and accuracy of 90.5%, 85.7%, and 88.1%, respectively [65]. The diagnostic criteria for chronic pancreatitis are based on the presence of major and/or minor features.

The major criteria for chronic pancreatitis are:

- Dilated main pancreatic duct >3 mm
- Hyperechoic foci with shadowing
- Stranding of the parenchyma with lobularity
- Cysts in the pancreas
- Ductal calculi
- Parenchymal calcifications

The minor criteria for chronic pancreatitis are:

- Dilated side branches of the pancreatic duct
- Irregular pancreatic duct contour
- Echogenic foci without shadowing
- Parenchymal lobularity without stranding

The presence of at least one major or two minor criteria is required to make a diagnosis of chronic pancreatitis using the Rosemont classification system [62]. The presence of 5 or more EUS criteria strongly suggests the diagnosis of CP [66].

Interobserver agreement is an issue in the diagnosis of chronic pancreatitis with EUS [67]. With the Rosemont classification, interobserver agreement could be improved in one study [68]. Other studies showed that the Rosemont classification does not improve accuracy and interobserver agreement compared to the conventional classification among experienced endosonographers [69, 70].

In a retrospective evaluation of the Rosemont criteria based on histopathology, the Rosemont classification was strongly predictive of chronic pancreatitis in patients with features suggestive (5 minor criteria or 3 minor criteria plus 1 major) of chronic pancreatitis. Herein, also a substantial agreement between conventional and Rosemont criteria was reported [71]. Although the Rosemont classification needs some routine to be applied regularly in clinical practice, this classification seems to be more accurate in excluding clinically relevant chronic pancreatitis [63]. The prevalence of EUS morphologic changes suggestive for chronic pancreatitis is lower in healthy subjects when the Rosemont classification is applied.

Aside from the classification systems, particular care should be given in the evaluation of the main pancreatic duct, particularly in non-calcifying chronic pancreatitis. In one study correlating EUS with histopathology after total pancreatectomy, on multiregression analysis, a main pancreatic duct irregularity was the only independent EUS feature that predicted chronic pancreatitis [72]. Thus, ductal main pancreatic duct dilation as the dilation of the accessory ducts are criteria for diagnosis of chronic pancreatitis, particularly if the duct course is irregular with a hyperechoic edge [73, 74]. A slight dilation of the pancreatic duct is also seen in older patients and is often a normal variant (see chapter on pancreatic age-related changes in this issue). If a significant dilation of the pancreatic duct is seen, an obstructive process should be excluded (like pancreatic head formations, ampullary process, bile duct disease). In case of duct dilation, an IPMN should also be taken into account for differential diagnosis, and care should be taken to visualize small polypoid structures originating from the ducts' walls [75, 76].

According to recent comparison between EUS features and histology on pancreatic specimen, lobularity reflects a more advanced histological stage (i.e., higher degree of inflammation, fibrosis, and atrophy) than the presence of hyperechoic foci and stranding, which can also be found in lower grade inflammation stages [77]. The evaluation of the strain ratio using quantitative EUS elastography allows for the quantification of pancreatic fibrosis and may help diagnose chronic pancreatitis. In one study which compared EUS elastography with histology, a strain ratio cut-off of 2.25 yielded an accuracy of 91% [78] and predicted pancreatic exocrine insufficiency [79]. EUS-guided biopsy for histological diagnosis of early chronic pancreatitis has a low diagnostic yield and a non-negligible risk of complication, so it is not suggested for the workup of chronic pancreatitis [75].

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a rare form of steroid-responsive chronic pancreatitis which shows particular histological features that were described in the Honolulu consensus document [80]. Diagnosis is supported by the International Consensus Diagnostic Criteria (ICDC) [81]. Imaging cannot distinguish between the histological subtypes, but a focal form, which mimics cancer, can be distinguished from the "diffuse sausage-like" appearance. EUS is not mandatory to diagnose AIP but gives additional information about the fine structural changes of the pancreatic parenchyma. On EUS, the diffuse form of AIP shows hypoechoic swelling with hyperechoic strands, extrahepatic duct and gallbladder thickening, lymphadenopathy, and a duct-penetrating sign – a smooth narrowing of the main pancreatic duct passing through the pancreatic mass [82]. On CE-EUS, a diffuse iso-enhancement is seen, with late-phase iso or hyperenhancement [83]. Elastography shows a homogenous hard (blue) elastographic pattern of the whole pancreas [84]. Early-stage AIP shows lobularity and hyperechoic pancreatic duct margins [85]. The course of the disease is characterized by spontaneous resolution or response to therapy with corticosteroids. Hyperechoic strands and lobularity improve after approximately 2 weeks of steroid therapy [86]. Late stage

AIP shows irreversible fibrotic changes with calcifications and formation of cysts, which rarely respond to corticosteroid therapy [87]. Histological diagnosis of AIP with EUS is challenging and requires large fragments (>10 mm) of tissue, preferably done with Franseen-type and Fork-tip-type fine biopsy needles, which are superior to FNA results [76, 88].

EUS for Accessing the Pancreatic Duct

In experienced hands, EUS enables direct pancreatic duct access in case of failed pancreatic duct cannulation during ERCP due to duodenal stenosis, ampullar process, pancreatic duct stricture, or altered postsurgical anatomy [89]. Herein, the pancreatic duct is accessed transgastrically or trans-duodenally via a 19- or 22-gauge needle. After performing a pancreatogram, a guidewire is inserted. The guidewire can be used for the placement of stents [90] or advanced to the papilla for performing a rendezvous procedure with a duodenoscope or colonoscope [91]. In such cases, EUS-guided pancreatic duct access can relieve obstructive symptoms of main pancreatic duct stenosis, is able to treat intraductal stones [92], or provide the drainage of pancreatic fistulas that do not resolve spontaneously or are not accessible via papilla [93].

EUS as a Screening Tool in High-Risk Patients for Pancreatic Cancer

For the screening of high-risk individuals for pancreatic cancer, guidelines suggest screening with EUS and MRI [94, 95]. The goal is to identify high-grade dysplastic precursor lesions and T1N0M0 pancreatic cancer. One prospective cohort study reported a benefit of screening on long-term survival [96]; another study emphasizes the weakness of imaging techniques in the detection of precursor lesions and in the follow-up of growing cysts, resulting in a failure to detect early pancreatic cancer or an overtreatment of precursor lesion with unnecessary surgery [97]. The limit of the aforementioned prospective studies is, despite the long follow-up and the high number of high-risk individuals screened (between 300 and 1,100 patients), the limited number of newly diagnosed pancreatic cancer cases (about 10 patients in every study, i.e., a pancreatic cancer incidence of 4.7% after 10 years of screening). Although the study of Overbeek et al. [98] found that EUS detected more solid lesions than MRI with a diagnostic yield of 100%, in the evaluation of cystic lesions smaller than 1 cm, MRI outperformed EUS.

Among patients with high-risk hereditary pancreatitis, like those with PRSS1 mutation, surveillance is also suggested. However, it was not established which method was the best [99]. EUS presents some weakness in the differentiation of chronic inflammatory changes, preneoplastic lesions, and malignancy [99–101]. As stated by the study of Overbeek et al. [98], EUS seems to be better than MRI for the timely detection of solid lesions, but less sensitive for cystic lesions, so combinations of these two modalities should be applied [102].

Conclusion

Overall, endosonography plays a valuable role in the diagnosis, characterization, and management of pancreatic disease and inflammation, or even as a screening procedure for pancreatic cancer in high-risk patients. It combines both imaging and interventional capabilities, making it an essential and uniquely versatile tool in pancreatology.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Francesco Vitali wrote the manuscript. Sebastian Zundler, Daniel Jesper, Deike Strobel, Dane Wildner, Nicoló de Pretis, Luca Frulloni, Stefano Francesco Crinó, and Markus F. Neurath critically revised the manuscript.

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