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Diagnostic Endoscopic Ultrasound in Pancreatology: Focus on Normal Variants and Pancreatic Masses

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Endoscopic ultrasound · Pancreatitis · Pancreatic cancer · Contrast-enhanced endoscopic ultrasound · Elastometry

Abstract
Background: Endoscopic ultrasound (EUS) is a main tool in gastroenterology for both diagnosis and exclusion of pancreatic pathology. It allows minimally invasive assessment of various diseases or anatomic variations affecting the pancreas also with the help of new Doppler technologies, elastography, contrast-enhanced imaging including post hoc image processing with quantification analyses, three-dimensional reconstruction, and artificial intelligence. EUS also allows interventional direct access to the pancreatic parenchyma and the retroperitoneal space, to the pancreatic duct, pancreatic masses, cysts, and vascular structures. ***Summary:*** This review aimed to summarize new developments of EUS in the field of pancreatology. We highlight the role of EUS in evaluating pancreatic pathology by describing normal anatomic variants like pancreas divisum, pancreatic lipomatosis, pancreatic fibrosis in the elderly and characterizing pancreatic masses, both in the context of chronic pancreatitis and within healthy pancreatic parenchyma. EUS is considered the optimal imaging modality for pancreatic masses of uncertain dignity and allows both cytological diagnosis and histology, which is essential not only for neoplastic conditions but also for tailoring therapy for benign inflammatory conditions. ***Key Messages:*** EUS plays an indispensable role in pancreatology and the development of new diagnostic and interventional approaches to the retroperitoneal space and the pancreas exponentially increased over the last years. The development of computer-aided diagnosis and artificial intelligence algorithms hold the potential to overcome the obstacles associated with interobserver variability and will most likely support decision-making in the management of pancreatic disease.

Introduction

Endoscopic ultrasound (EUS) is a fundamental tool for the diagnosis as well as for therapeutic procedures in gastroenterology, hepatology, and pancreatology. It combines the advantage of endoscopy to gain the access to the gastrointestinal tract with the features of high-frequency ultrasound (US) probes to achieve superior visualization of adjacent anatomical regions like the pancreas.

The visualization of the pancreatic gland through imaging in the daily routine is challenging due to its retroperitoneal location. To maximize patients' safety and avoid unnecessary costs, pancreas imaging is usually performed noninvasively adopting a step-up approach.

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Transabdominal US is a widespread first-line tool for the evaluation of the pancreas [1, 2]. However, this modality has some drawbacks due to operator and patients related factors [3]. Transabdominal US is useful as a screening method, but systematic visualization of pathologies or lesions is not always possible. As a second step, cross-sectional imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used [1].

Sometimes, the results of the above-mentioned examinations are not conclusive, and EUS is performed to examine the pancreatic parenchyma. EUS is an endoscopic imaging modality which provides the highest spatial resolution of the pancreas compared with CT or MRI [4, 5]. This is possible due to the proximity to the pancreas to the US transducer, which is located on the tip of the flexible endoscope [6]. EUS examination can be performed either with a radial or linear transducer. Linear EUS performs imaging in the same plane as the shaft of the endoscope, whereas radial EUS offers a panoramic circumferential view perpendicular to the shaft of the endoscope. EUS miniprobes can be inserted in the working channel of several endoscopes and can be used to perform intraductal US within the bile duct or pancreatic duct. Miniature probes are available in a variety of frequencies, outer diameters, and tip designs [7]. They can be useful for the evaluation of subepithelial lesions, but their use is not widespread commonly used due to limited durability and high price. EUS is performed guiding the transducer next to the pancreas by positioning the scope in the stomach, bulb, and second portion of the duodenum and by eliminating the artifacts of intestinal gas with suction, instillation of water, or by filling the balloon on the echoendoscope with water.

Strength and Limitation of EUS in Pancreatology

EUS is currently considered the most advanced technique for the diagnosis of pancreaticobiliary diseases in terms of spatial resolution, especially for the evaluation of the parenchyma and the secondary pancreatic ducts [8]. The two major limitations of EUS preventing it being the "gold standard" technique for primary assessment of pancreatic diseases are the lack of standard criteria to be used and the operator-dependent acquisition of high-quality images. Visualization of the pancreatic gland can be heterogeneous, mainly due to anatomical issues and parenchymatous properties such as fibrosis, fat content, or calcifications that may induce some degrees of acoustic shadowing [9]. Moreover, accuracy seems to be lower in the tail of the pancreas [10, 11]. However, EUS is still considered the best diagnostic technique for the detection of small pancreatic processes [4, 12, 13].

EUS is difficult to learn; therefore, teaching has to be standardized [14]. Several guidelines for the assessment of competency in EUS have been published by several GI societies [15–19]. Before independent practice, ESGE recommends a procedure volume of more than 250 cases per year with satisfactory visualization of key anatomical landmarks in more than 90% of the cases [20].

The other side of the medal in having high-resolution imaging of the pancreatic features available is the need for differentiation between normal variants and the early stages of disease. This has been demonstrated in the evaluation of the minimal-change chronic pancreatitis and in the follow-up of high-risk individuals for pancreatic cancer [21]. Here, it was not possible to differentiate between physiological age-related pancreatic morphological changes and early signs of pancreatic chronic inflammation [22]. In addition, structural alterations due to fibrotic changes after an acute pancreatitis cannot be differentiated between an early form of a chronic pancreatitis or age-related fibrotic changes.

It should be kept in mind that EUS is an invasive procedure that entails minimal lethality risk [23]. It requires conscious sedation or even tracheal intubation in high-risk patients, particularly in therapeutic procedures with aspiration risk [24]. Complications are associated with underlying disease, the general health condition of the patient, and the type of echoendoscope chosen. Among patients with gastric outlet obstruction, a complete EUS is not possible. General perforation risk is estimated to be 0.03–0.06% [25, 26]. Perforations are mostly localized in the mid and lower esophagus and in the duodenal bulb. After EUS fine-needle aspiration (FNA), perforation risk increases up to 6.3% [27]. Bleeding after diagnostic EUS is rare (0–1.4%); however, after therapeutic or diagnostic biopsy procedures, the incidence of bleeding increases, with the maximal risk having been described for intracystic microforceps biopsy [12, 28, 29] and in patients receiving antithrombotic agents [30, 31]. Acute pancreatitis is described after FNA/FNB and after advanced procedures like RFA [32]. EUS-FNA of solid pancreatic masses is infrequently associated with pancreatitis [33–35]. For pancreatic cysts, FNA pancreatitis occurs in up to 2% of the cases [36, 37]. In one recent study, it was shown that the risk of pancreatitis after EUS-FNA in branch-duct IPMN is 6 times higher compared to those with other types of cysts [38]. Due to the risk of superinfection, antibiotics are mandatory during invasive procedures of pancreatic cysts [39]. No increased risk was shown if trainees were performing the FNA procedure [40]. A rare complication of EUS-guided sampling is tumor cell seeding [41, 42]. The majority of published cases report that tumor cell seeding occurs after multiple passes. However, considering the low number of studies on the topic, a clear correlation between tumor seeding and the needle type or the number of passes cannot be ascertained [43].

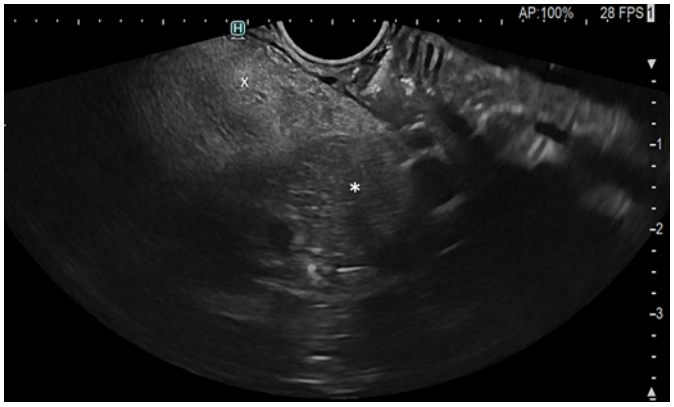

Fig. 1. Visualization of the different echogenicity between the hypoechoic ventral split (*) and the hyperechoic lipomatotic pancreatic head (X) with linear EUS.

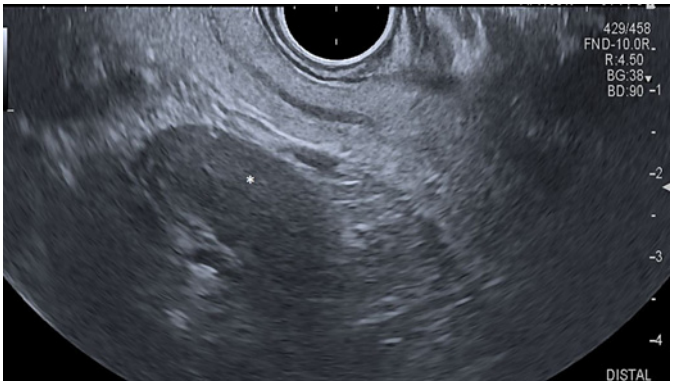

Fig. 2. Pancreas lipomatosis. EUS showing the pancreas body from gastric position with a regular not dilated pancreatic duct. Increased echogenicity of the pancreatic parenchyma compared to the kidney (*) defines pancreatic FI or lipomatosis.

Role of EUS in Diagnosis of Anatomic Variants of the Pancreas

Pancreatic parenchyma normally appears homogenous with salt-and-pepper texture, and the contour of the pancreas is normally smooth without significant lobularity. Echogenicity tends to increase with age and with obesity (see chapter pancreatic lipomatosis).

The main pancreatic duct appears as a linear anechoic structure with hyperechoic walls. Its normal caliber ranges from 3 mm in the head to 1 mm in the pancreatic tail. Side branches can be visualized with EUS in healthy patients. In up to 17% of the patients undergoing EUS for a non-pancreatic indication, i.e., patients without clinical signs or suspicion of pancreatic disease, pancreatic abnormalities are detected by EUS [44]. These results suggest that cautious interpretation of EUS findings for early changes of pancreatic parenchyma is necessary. For a definitive diagnosis of a chronic pancreatic inflammatory disease, namely, chronic pancreatitis, a minimum of 2 criteria are needed [45] in order not to overinterpret subtle changes of unclear clinical significance, which may be age-related or induced by exogenic noxae [22, 46]. In the next chapters, we will discuss some anatomical variants that are usually visualized during EUS and should be distinguished from pathological findings.

The Visualization of the Ventral and Dorsal Split of the Pancreas

Pancreatic imaging with transabdominal US and EUS can detect differences in echogenicity in the pancreatic parenchyma that is derived from the ventral pancreatic split (ventral anlage, Fig. 1) [47]. This can be explained by the diminished fat content of the ventral bud [48, 49]. An endosonographic border between the hypoechoic ventral part and a brighter dorsal anlage can be seen in up to 75% of the patients [47]. It is important not to interpret the ventral anlage as a pancreatic mass [50]. On the other hand, as shown in the *NEST* case series, a prominent demarcation between the ventral and dorsal anlage may make the detection of pancreatic masses more difficult, with the risk of overseeing malignancy [51]. In such cases, close follow-up of the suspected lesion should be offered, since also experienced endosonographers have been shown to oversee cancer arising in this area [51].

Pancreatic Lipomatosis and Pseudolipomatous Hypertrophy

Pancreatic lipomatosis (PL) is defined as the fatty infiltration (FI) of the pancreatic parenchyma [52]. The degree of FI on EUS is typically estimated by comparison of the echogenicity of the pancreas with the surrounding organs such as the spleen and kidneys [53] (Fig. 2). The fat itself does not determine the echogenicity, but the architectural modification due to alternation of glandular and fatty interfaces is responsible for the hyperechoic image [49]. EUS can detect subtle differences in fat in various tissues, such as the liver, where areas of circumscribed steatosis are better detected than with CT [54, 55]. PL represents the most frequent benign condition of the adult pancreas [56]. The reported prevalence varies from 16% in the healthy population up to 61% in patients with comorbidities like diabetes mellitus or metabolic syndrome [53, 57–59]. It can be either diffuse or focal and can be a dynamic process with the possibility of progression or regression over time [60]. Some patients develop exocrine pancreatic insufficiency and some degree of pancreatic fibrosis or even chronic pancreatitis [61]. The extreme variant is pseudolipomatous hypertrophy. This condition is very uncommon. It is often associated with syndromes like Shwachman-Diamond or cystic fibrosis. It can also be clinically discovered as a mass or pseudotumor, particularly if it is associated with an enlargement of the pancreas [62, 63]. If EUS visualization depth is impaired due to the

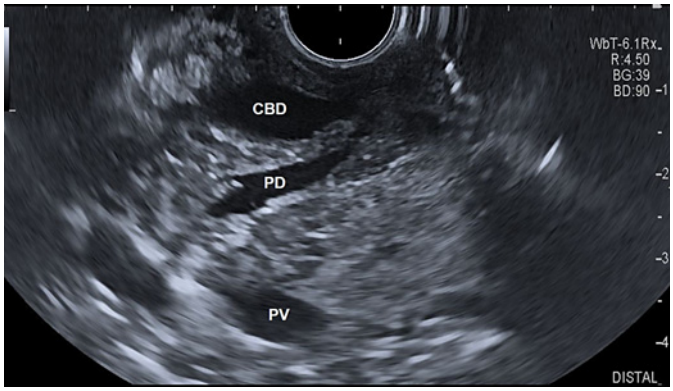

Fig. 3. EUS of the papillary region with normal anatomical visualization of the stack sign (CBD, common bile duct; PD, pancreatic duct; PV, portal vein).

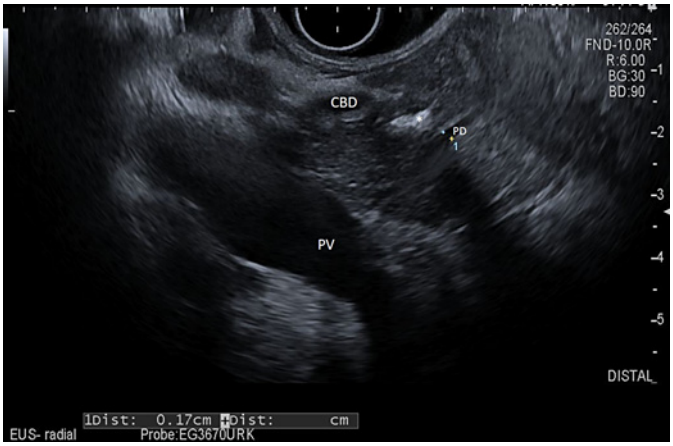

Fig. 4. EUS of a PD with calcifying chronic pancreatitis. EUS diagnosis is supported by the lack of the stack sign (CBD, common bile duct; PD, pancreatic duct; PV, portal vein; *calcification).

hyperechoic appearance of FI, cross-sectional imaging usually leads to a definitive diagnosis [50]. However, in rare cases, histological confirmation to rule out liposarcoma may be necessary [64].

Pancreas Divisum

Pancreas divisum (PD) is the most common congenital anomaly of the pancreas. Among MRCP and autopsy studies, the prevalence in the general population is about 8% [65].

Due to the failure of the fusion of the ventral and dorsal pancreatic splits during embryological development, the dorsal duct becomes the main channel of drainage for pancreatic secretion from the body and tail regions of the pancreas. PD is common in the general population and asymptomatic [66]. However, it is a matter of debate if PD may play a role in the development of recurrent acute or chronic pancreatitis as a "two-hit" phenomenon in case of predisposing factors like gene mutations [67, 68]. There are three types of PD. Type 1 (classic PD) is the complete failure of fusion of the ducts of Santorini and Wirsung, type 2 is the absence of the duct of Wirsung, and type 3 (incomplete PD) is the presence of a tiny communication between the dominant dorsal duct (Santorini) and the main pancreatic duct [69].

The diagnosis of PD is usually made in the evaluation of patients with idiopathic or recurrent acute pancreatitis [66]. As a step-up approach, MRCP to evaluate ductal abnormalities is most commonly performed. EUS, differently to ERCP, allows detailed evaluation of the pancreaticobiliary ductal system without injecting contrast medium. Retrospective studies analyzed the efficacy of EUS for diagnosis of PD with overall accuracy of up to 97% and moderate positive predictive value of 80% [12, 70, 71]. PD can be accurately excluded if the main pancreatic duct can be visualized backwards from the head to the body around the genu [71]. In experienced hands, linear EUS has been shown to have a sensitivity of 95% and an overall accuracy of 97% for the diagnosis of PD when the main pancreatic duct can be well visualized [70].

On radial endosonography, absence of the "stack sign" has been suggested as a useful criterion for diagnosing PD [72]. This sign is shown from the duodenal bulb with the inflated balloon, visualizing in parallel the distal common bile duct, ventral pancreatic duct, and the portal vein in parallel being stacked together (Fig. 3). The bile duct is the closest to the transducer. Other signs are the "crossed duct sign" (bulb view showing Santorini duct crossing the common bile duct) [69]. The diagnosis of PD can be suggested by negative stack sign or positive cross duct sign (Fig. 4). A dominant Santorini duct (a Santorini duct diameter more than the ventral pancreatic duct diameter) can also be a sign of PD. The diagnosis of PD is excluded if the pancreatic duct can be visualized continuously from the major papilla and shows the ventral-dorsal transition from the hypoechoic ventral anlage to the hyperechoic dorsal bud [69, 70].

Intrapancreatic Accessory Spleen

Intrapancreatic accessory spleen (IAS) is an infrequent congenital finding that may mimic other pancreatic pathologies (particularly neuroendocrine tumors) and sometimes could be a cause of unnecessary distal pancreatic resection [73]. The prevalence is lower than 1% in the general population [74]. Rodriguez et al. [75] described IAS as a homogeneous, well-defined, round, isoechoic or hypoechoic mass with smooth borders on EUS. Kim et al. [74] reported only a fair (Kappa 0.37) interobserver agreement in judging IAS as a pancreatic lesion or not. They also reported that the sensitivity and specificity of EUS for IAS were greater than 70% [74]. However, in some cases, where the suspicion of pancreatic neuroendocrine neoplasm

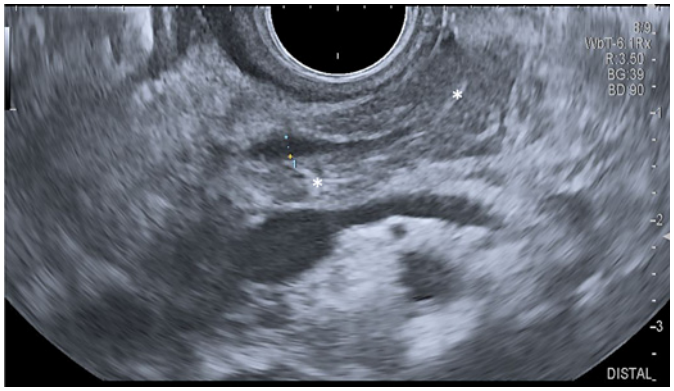

Fig. 5. Example of a pancreas in elderly patients. The pancreatic duct (1) is irregular with slight proximal dilation without an obstructive cause. The pancreatic parenchyma shows hyperechoic foci which correspond to fibrosis (*). Other hyperechoic spots correspond histologically to FI, which can be diffuse (see Fig. 2) or focal.

(NET) is high and if combined imaging modalities like EUS, MRI, CT, or PET are not conclusive, EUS-FNA is required to establish definitive diagnosis. Usually, due to the small size of the lesion, vascularization patterns cannot be sufficiently distinguished from a small pancreatic NET. Some older reports described a prolonged enhancement (up to 3–5 min) on the delayed hepatosplenic phase during contrast-enhanced US imaging [76, 77]. In case of doubt, it is suggested to perform dynamic real-time EUS imaging with careful transducer movement, and in some cases, the connection to the spleen with a bridge of splenic tissue can be shown, which is called "the bridge sign" [78].

Pancreatic Fibrosis in the Elderly

During aging, the pancreas shows changes similar to those observed in chronic pancreatitis including calculi, main pancreatic duct dilation or narrowing [46] and FI [79] in the examination with EUS (Fig. 5). Increasing fibrosis with age is also pointed out by EUS-guided semiquantitative elastography that revealed that the pancreas becomes significantly stiffer with increasing age [80], in line with the findings of pathological studies [81].

EUS for the Differential Diagnosis of Pancreatic Masses

Pancreatic cancer is one of the most lethal malignancies worldwide, with a low survival rate due to its late diagnosis [82]. Studies have shown that EUS can detect small pancreatic lesions that may not be detected by other imaging techniques such as CT or MRI [4], particularly when they are smaller than 3 cm [83]. Moreover, EUS-guided FNA can provide a histological diagnosis of suspicious lesions [12]. In addition, enhanced imaging techniques further aid in the evaluation of pancreatic masses, e.g., elastography (that measures the relative stiffness of tissues based on its resistance to compression) [84] and contrast-enhanced EUS [85] or artificial intelligence [86]. Some promising observations have also been made with new color Doppler techniques for the differentiation between pancreatic adenocarcinoma and chronic pancreatitis [87]. A recent meta-analysis for CE-EUS showed a pooled sensitivity, specificity, and AUROC of 94%, 89%, and 0.97 for the diagnosis of pancreatic adenocarcinoma [88]. CE-EUS combines the advantage of high-resolution US with the ability to visualize micro- and microvasculature without extravasation of contrast medium into the interstitium. This enables a superior visualization of vascularization patterns compared to all other imaging modalities [89, 90].

An adequate US machine for CE-EUS (equipped with low-MI contrast imaging mode) is needed. The recommended dose of contrast medium (i.e., for SonoVue® is 4.8 mL under most circumstances) according to the manufacturer should be applied. For extravascular applications (i.e., visualization of cavities and ducts), a few drops of contrast medium can be diluted in 10–100 mL saline solution [89].

The results of contrast-enhanced EUS can be objectivized using software quantifying the enhancement of contrast medium with time-intensity curves [91]. A particular role of EUS has been suggested for the differentiation of focal inflammatory masses that can present with a hypoechoic appearance in B-mode EUS and may exhibit diffuse iso/hyperenhancement using CE-EUS [92]. Such hyperenhancement can be helpful to distinguish focal autoimmune pancreatitis and pancreatic cancer since inflammatory diseases usually show some degree of enhancement [93–95]. CE-EUS combined with elastography plays a fundamental role in complementary diagnostic of focal pancreatic masses [96]. However, due to a specificity lower than 90%, the authors recommend to combine imaging and biopsy techniques for a correct diagnosis. Metastases to the pancreas, synchronic or metachronic, can also show hyperenhancement – like in renal cell carcinoma metastasis – so in such cases, histology may be required [97, 98].

Several other solid lesions can undergo cystic degeneration. This latter category accounts not only for pancreatic carcinomas with compression of the pancreatic duct but also for pancreatic cystic NETs, degenerated IPMN with sign of malignancy, where a solid hypoenhancing component or nodes are detected, and solid pseudopapillary neoplasms. On EUS, NET shows hyperenhancement on CE-EUS, also in case of cystic appearance [99, 100], while solid pseudopapillary neoplasms more frequently shows calcifications, isoechogenicity, or hyperechogenicity, as well as an isoechoic or hypoechoic

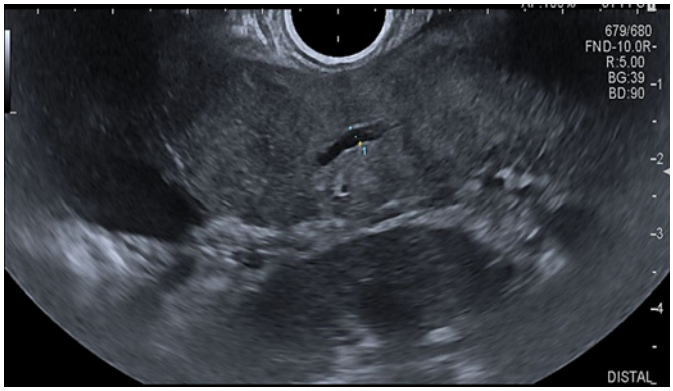

Fig. 6. EUS in the transgastric position showing an autoimmune pancreatitis before steroid therapy. The pancreatic body is "sausage"-like enlarged with hypoechoic areas. The main pancreatic duct (1) is not dilated with hyperechoic borders.

vascular pattern or the presence of the alveolus nest sign on contrast medium US [101]. The evaluation and differential diagnosis of other pancreatic cystic lesion is outside the scope of this review, and we refer to current guidelines on management of pancreatic cysts [102–104].

Contrast medium also plays a role in guiding tissue acquisition by EUS as it enables diagnosis with a lower number of fine-needle passes [105, 106]. For EUS-guided tissue acquisition, different needle sizes from 19 to 25 gauge are available. Smaller needles may be more easily directed to a target lesion, particularly in lesion located deep in the GI tract. A recent meta-analysis showed that EUS fine-needle biopsy was more accurate than EUS-FNA (where cytology only is evaluated) to diagnose pancreatic cancer [107, 108] and non-pancreatic lesion [109]. Among fine-needle biopsy needles, Franseen and fork-tip needles showed the highest performance for tissue sampling in the evaluation of pancreatic masses [109, 110].

New techniques are awaited since all the aforementioned techniques have limitations in the context of calcification or long-standing chronic pancreatitis. A special rare type of focal chronic pancreatitis that have to be distinguished from autoimmune pancreatitis (Fig. 6) is paraduodenal pancreatitis. It represents a diagnostic challenge for endosonographers and pancreatologists since due to the frequent occurrence of duodenal obstruction, cystic lesions in the duodenal wall, or calcifications, EUS is not able to play to its strengths. This makes the differential diagnosis with pancreatic groove carcinoma, low-differentiated neuroendocrine carcinoma, and duodenal adenocarcinoma difficult since also histology usually cannot help in diagnosis of paraduodenal pancreatitis [50, 111]. Moreover, it should be remembered that chronic pancreatitis itself is a risk factor for pancreatic cancer and, on the other hand, a cause of pancreatitis can be the pancreatic duct obstruction by a pancreatic neoplasm [112].

An additional tool that requires further validation is real-time EUS-guided confocal endomicroscopy. After an inconclusive biopsy results, this new technique could help rule out malignancy and unnecessary surgery [113]. A new promising but not yet widespread imaging technique is three-dimensional contrast-enhanced EUS. It may play a role in cancer to depict the relationship of vessels, bile duct, pancreatic duct, and the primary lesion to evaluate resection [114].

Conclusion

During the past decade, the use of EUS deeply developed and it has now a significant impact and the highest role in clinical diagnostics and therapy in pancreatology. The rapid increase in the development of several diagnostic tools makes EUS an outstanding unique technique in the evaluation of pancreatic diseases that cannot be replaced from alternative cross-sectional imaging techniques.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Author Contribution

Francesco Vitali wrote the article. Sebastian Zundler, Daniel Jesper, Dane Wildner, Deike Strobel, Luca Frulloni, and Markus F. Neurath critically revised the manuscript.

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