Endoscopic Ultrasound Management of Pancreatic Lesions

From Diagnosis to Therapy

Antonio Facciorusso
Nicola Muscatiello
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Foreword

Once upon a time, in the land of *Radiology*, there was a girl called *Ultrasound*. *Ultrasound* had free access to the liver, but no chance to explore the pancreas. One day, *Ultrasound* met a prince, called *Endoscopy*, and fell in love. The wedding was celebrated by Dimagno et al. who published in *Gastroenterology,* in 1982, a preliminary experience with endoscopic ultrasonography in 32 patients. Then, in less than 40 years, "Cinderella" *Ultrasound,* together with "prince" *Endoscopy,* became a powerful queen in the field of Pancreatology. That queen is now called Endoscopic Ultrasound (EUS) and is currently included in all guidelines of solid and cystic pancreatic lesions.

EUS has dramatically changed over time. A breakthrough that paved the road of interventional EUS was the first EUS-guided fine-needle aspiration performed with a needle prototype and published in 1992 by Peter Vilmann et al. To date, according to NCCN, ESMO, and ESGE guidelines EUS is the procedure of choice for tissue sampling of solid pancreatic lesions. Similarly, new tools like microforceps and confocal laser endomicroscopy are emerging with significant improvement of diagnostic accuracy in defining pancreatic cystic lesions, as compared with traditional cyst fluid cytology. However, the most relevant metamorphosis of EUS is happening right at the very moment: EUS is moving from a diagnostic to a therapeutic procedure. Besides the already well-defined role in peripancreatic fluid collection drainage, EUS serves as guidance for radiofrequency or laser ablation of pancreatic solid and cystic neoplasms and for drainage of bile and pancreatic ducts when ERCP fails or is not feasible.

As a powerful vehicle, EUS needs an expert pilot. Endoscopists performing pancreatic EUS must first be familiar with pancreatic diseases; second, they need to be skilled both in ultrasound and endoscopy. This book, titled *Endoscopic Ultrasound Management of Pancreatic Lesions—From Diagnosis to Therapy*, edited by Antonio Facciorusso and Nicola Muscatiello, is organized into twenty chapters covering the entire spectrum of applications of EUS for the management of pancreatic neoplasms and will drive the reader along a path that originates from pancreatic diseases and continues on to the field of diagnostic and therapeutic EUS.

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Overview of Pancreatic Masses and Cystic Lesions

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Raffaele Pezzilli

1.1 Introduction

A wide spectrum of benign and malignant diseases can produce a mass in the pancreas; these diseases can be solid benign (such as mass-forming chronic pancreatitis) or, more frequently, malignant (ductal adenocarcinoma, endocrine tumors), or cystic (cystic neoplasms, true cysts, or pseudocysts). The most important question is whether or not it is a malignant or a benign tumor; whenever possible, in the majority of the cases that are fit for treatment, histological confirmation of the diagnosis of malignancy is necessary. Of course, the major interest in routine clinical practice is in diagnosing and treating benign and malignant tumors; a systematic classification of pancreatic solid and cystic masses has been recently reported by the World Health Organization (Table 1.1) [1, 2]. Pancreatic neoplasms originate from epithelial cells, neuroendocrine cells, and mesenchymal tumors, and they can be benign, premalignant, or malignant; the pancreas can also be involved in lymphomas and solid tumors of distant organs. The aim of this review was to describe the clinical signs of solid and cystic lesions as well as the imaging aspect in order to reach an appropriate diagnosis, and the respective treatment and follow-up.

1.2 Epidemiological Aspects

The incidental finding of a solid pancreatic mass is quite rare while the occasional finding of a pancreatic cystic nodule is rather common [3]. There is no doubt that the majority of the symptomatic pancreatic masses are pancreatic cancer which is an intractable malignancy and is the seventh leading cause of global cancer deaths in industrialized countries [4]. Based on GLOBOCAN 2018 estimates, pancreatic

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Table 1.1 World Health Organization (WHO) 2010 classification of solid and cystic lesion of the pancreas [1, 2]

Epithelial tumors
Benign
Acinar cell cystadenoma
Serous cystadenoma
Premalignant lesions
Pancreatic intraepithelial neoplasia, grade 3 (PanIN-3)
Intraductal papillary mucinous neoplasm (IPMN) with low- or intermediate-grade dysplasia
Intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia
Intraductal tubulopapillary neoplasm (ITPN)
Mucinous cystic neoplasm (MCN) with low- or intermediate-grade dysplasia
Mucinous cystic neoplasm (MCN) with high-grade dysplasia
Malignant lesions
Ductal adenocarcinoma
Adenosquamous carcinoma
Mucinous adenocarcinoma
Hepatoid carcinoma
Medullary carcinoma
Signet ring cell carcinoma
Undifferentiated carcinoma
Undifferentiated carcinoma with osteoclast-like cells
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma
Mixed acinar ductal carcinoma
Mixed acinar neuroendocrine carcinoma
Mixed acinar neuroendocrine ductal carcinoma
Mixed ductal neuroendocrine carcinoma
Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma
Pancreatoblastoma
Serous cystadenocarcinoma
Solid pseudopapillary neoplasm
Neoplasms of the neuroendocrine pancreas
Nonfunctioning (nonsyndromic) neuroendocrine tumors
Pancreatic neuroendocrine microadenoma
Nonfunctioning pancreatic neuroendocrine tumor
Insulinoma
Glucagonoma
Somatostatinoma
Gastrinoma
VIPoma
Serotonin-producing tumors with and without carcinoid syndrome

Table 1.1 (continued)

Serotonin-producing tumor
ACT-producing tumor with Cushing syndrome
ACTH-producing tumor with Cushing syndrome
Pancreatic neuroendocrine carcinoma (poorly differentiated neuroendocrine neoplasm)
Neuroendocrine carcinoma (poorly differentiated neuroendocrine neoplasm)
Small-cell neuroendocrine carcinoma
Large-cell neuroendocrine carcinoma
Mixed neuroendocrine non-neuroendocrine neoplasms
Mixed ductal neuroendocrine carcinoma
Mixed acinar neuroendocrine carcinoma
Mature teratoma
Mesenchymal tumors
Lymphangioma
Lipoma
Solitary fibrous tumor
Perivascular epithelioid cell neoplasm (PEComa)
Ewing sarcoma
Desmoplastic small round cell tumor
Lymphomas
Diffuse large B cell lymphoma (DLBCL)
Follicular lymphoma
Lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
T cell lymphomas
Secondary tumors

cancer has been ranked as the 11th most common cancer in the world counting 458,918 new cases and causing 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 [4]. The worldwide incidence of and mortality from pancreatic cancer correlate with increasing age and are slightly more common in men than in women [4]. Its incidence is estimated to increase and will include 355,317 new cases by 2040. A slight difference in pancreatic cancer incidence among genders as well as a significantly different geographic distribution has been observed [4]; it is more common in men (5.5 per 100,000; 243,033 cases) than in women (4.0 per 100,000; 215,885 cases). Finally, the incidence rate for both genders increases with age [4]. The mortality rate is also high; in 2018, the highest mortality rates were recorded in Western Europe (7.6 per 100,000 people), Central and Eastern Europe (7.3 per 100,000 people), and followed by Northern Europe and North America (equally 6.5 per 100,000 people) [4]; a trend towards an increase in pancreatic cancer incidence (+77.7% with 356,358 new cases) and mortality (+79.9%, 345,181 deaths) has been predicted from 2018 to 2040 [4]. Even if the mortality/incidence ratio from 2014 to 2018 was 94%, the five-year survival rate for pancreatic cancer increased from 6% to 9% which shows that some progress has been made [4].

The prevalence of incidentally discovered pancreatic cysts detected by computed tomography (CT) or magnetic resonance imaging (MRI) is approximately 3% [5, 6], increasing up to 9% when using high-resolution MRI [7]; this rate can be as high as 20–40% when considering only elderly people. The most represented incidentalomas are intraductal papillary mucinous neoplasia (IPMNs) and serous cystadenomas, although very small cystic lesions are difficult to characterize and small cysts may also disappear [8]. For a cystic mass or in the case of a cystic component, the most informative imaging technique is MRI; whereas, for a solid pancreatic mass, the in-depth imaging technique is CT. The prevalence of a solid pancreatic mass occasionally found at CT scan is quite low, ranging from 0.5 [9, 10] to 6% [11]. Correct diagnostic management is important for the diagnosis of a pancreatic solid nodule to assure the appropriate treatment of the patient in order to avoid over- and undertreatment. Therefore, the physician plays a pivotal role in coordinating the different specialists involved in the diagnostic process, such as endoscopists, pathologists, and radiologists. The differential diagnosis of a pancreatic solid nodule includes two different pathogenic etiologies: neoplastic or inflammatory/autoimmune. Neoplastic pancreatic nodules present great histological variability, and the likelihood of a diagnosis depends, for the most part, on the presence of symptoms rather than an incidental diagnosis. A diagnosis of malignancy is more probable in symptomatic rather than in asymptomatic cases [3]. The finding of a pancreatic mass associated with symptoms such as jaundice, weight loss, and back pain suggests a diagnosis of malignancy, with an incidence of pancreatic cancer in up to 80% of cases [12]. Conversely, in the case of the incidental diagnosis of a solid pancreatic nodule, the most common diagnoses are pancreatic neuroendocrine tumors (NENs), followed by pancreatic ductal adenocarcinoma, solid pseudopapillary tumors, and focal chronic pancreatitis (0–11%) [13].

1.3 Clinical Presentation

The size and anatomic location of the mass are crucial when determining the presence of clinical symptoms. A mass located in the head of the pancreas typically results in the obstruction of the biliary duct, leading to jaundice or pancreatic duct obstruction, with consequent pain and impairment in exocrine function; a mass in the body and tail of the pancreas is more often asymptomatic [14, 15]. If the pancreatic mass is a pancreatic NEN, in particular if it is functional, the symptoms are related to the hormone released (more often insulinomas and gastrinomas), making them usually easily recognizable [16]. An uncommon presentation of pancreatic nodules includes acute pancreatitis due to obstruction of the pancreatic duct, new onset or worsening diabetes in healthy adults, and incidental finding on abdominal imaging for unrelated diseases [17, 18]. On the contrary, the majority of cystic pancreatic neoplasms are usually asymptomatic [19, 20], and the appearance of symptoms similar to those of a solid mass may indicate malignant transformation [21].

1.3.1 Pain

Present in the majority of patients, pain is often the symptom which prompts the patient to seek medical attention. Typically, it arises as pain in the upper abdomen which radiates to the back or vague discomfort similar to indigestion which, however, does not respond to common drugs [22, 23]. Abdominal pain is present even if the mass is small (<2 cm), regardless of its location, although it has been reported by more patients having a mass in the body and/or tail of the pancreas (90%) as compared with those having cancer in the head of the pancreas (70%) [24]. The origin of the pain can be multifactorial; stretching of the pancreatic capsule and/or ductal stenosis or obstruction may contribute to its onset [25] as does liver capsule pain from metastatic liver disease. If the mass is a cancer, perineural invasion is the main cause of pain [26]. Interestingly, pain helps to predict a poor outcome in pancreatic adenocarcinoma while, in all other pancreatic malignancies in which neural invasion of cancer cells is not a key pathomorphological phenomenon, no association of pain and survival has been reported [27, 28].

1.3.2 Jaundice

Jaundice is caused by the extrinsic obstruction of the bile duct with excessively increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The absence of urobilinogen and stercobilinogen determines the pale stools and dark urine. Approximately 82% of patients with a mass in the head of the pancreas have so-called “painless jaundice” as a marked feature, and rising bilirubin levels can cause pruritus. When the tumor is in the head of the pancreas, it occurs in 80% to 90% of patients, while when the lesion arises in the body and tail, it is observed in approximately 6% of patients.

1.3.3 Weight Loss

The association of a pancreatic mass and weight loss is typical of pancreatic adenocarcinoma, and it may occur in the absence of jaundice or distant localization of the disease [29]. Among the numerous factors affecting normal nutritional support, patients may experience the onset of exocrine pancreatic insufficiency (EPI) before diagnosis, during nonsurgical treatment, and/or following surgery. Since testing is cumbersome, EPI is often recognized clinically and treated empirically [30].

In the end, malnutrition can lead to skeletal muscle wasting and fat degradation, longer hospital stays, and an increased risk of complications; it reduces response to the treatment and patient well-being while increasing the risk of morbidity and mortality in operated and non-operated patients [31–33].

1.3.4 Diabetes

Diabetes of new onset in patients with a pancreatic nodule should alert the physician to the possibility of a diagnosis of cancer, since almost 80% of pancreatic cancer patients have glucose intolerance or frank diabetes. The majority of cases of diabetes associated with pancreatic cancer are diagnosed either concomitantly with the cancer or during the 2 years before the cancer is found; 71% of the glucose intolerance found in pancreatic cancer patients is unknown before the cancer is diagnosed [34, 35]. Several studies have demonstrated that diabetes in pancreatic cancer patients is characterized by peripheral insulin resistance and that insulin sensitivity in patients who undergo tumor resection is markedly improved 3 months after surgery. Nonetheless, diabetes or impaired glucose tolerance often occurs in pancreatic NEN patients due to the tumor mass effect or because the hormones secreted by the tumor interfere with the glucose metabolism [36].

1.3.5 Nausea and Vomiting

Early satiety, nausea, and vomiting often occur in the case of a large mass, and they are usually related to compression on the second portion of the duodenum creating partial or complete obstruction [29], or to the delayed gastric emptying which often accompanies pancreatic nodules [37].

1.3.6 Signs of Malignant Transformation of Cystic Pancreatic Neoplasms

Assessing the following risk features is helpful in decision-making between the options of watchful waiting versus surgery. Patients with at least two of the following risk factors (such as lesion size greater than 3 cm which involves a threefold increase in malignancy risk, the presence of a mural nodule, and dilation of the main pancreatic duct) appear to be at risk for malignant progression, although the data supported by retrospective studies have demonstrated approximately a 15% chance of developing a pancreatic malignancy [38, 39]. Other factors may also be predictive of a higher risk of malignancy, such as a family history of pancreatic cancer (increases the risk of IPMN), mutations which predispose to pancreatic cancer (*BRCA2*), abnormal blood levels of carbohydrate antigen 19-9 (CA-19-9), unexplained acute pancreatitis (especially in patients over 50 years of age), recent onset diabetes mellitus, excess weight, and coarse calcification [40–46].

1.4 Genetic Mutations and Laboratory Markers

In the diagnostic workup of a pancreatic nodule, laboratory tests are useful in guiding the diagnosis and for a general evaluation of the patient. Laboratory tests can diagnose subclinical jaundice or signs of inflammation, guiding the subsequent

workup. In recent years, the genetic evaluation of patient status has been emphasized; for example, the most importance has been ascribed to the possibility of associated familial pancreatic cancer or a gene mutation capable of leading to the development of pancreatic cancer [47, 48]. Germline mutations of BRAC1/2 are present in 1–4.6% of pancreatic ductal carcinoma patients as compared to a prevalence of BRAC1/2 mutations in the general population of 1:400; it should be noted that a BRAC2 mutation is a common hereditary risk factor in outpatients with pancreatic tumors. Other mutations are related to the PALB2, CDKN2A, ATM, p53, MSH1, MSH2, and MSH6 genes. These mutations are rare but they have high penetrance; for example, the presence of CDKN2A increases the risk of developing a pancreatic ductal carcinoma 38-fold [49]. The distinction between neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) is also linked to their genetic background, as TP53 and RB1 inactivation in NECs sets them apart from NETs. A large number of genetic and epigenetic alterations have been reported, and recurrent changes have been traced back to a reduced number of core pathways, including DNA damage repair, cell cycle regulation, and the phosphatidylinositol 3-kinase/mammalian target of rapamycin signaling [50]. Finally, the presence of familial pancreatic cancer in cystic lesions of the pancreas suggests performing a resection due to the increased risk of developing a malignant transformation [21].

From a practical point of view, a wide variety of tumor markers derived from serum, pancreatic tissue, saliva, and/or stool and of different natures (tumor-associated antigens, hormones, enzymes, and immunoglobulins) have been evaluated during the diagnostic workup of a pancreatic nodule. Tumor markers have no utility in screening but could be an important tool during the differential diagnosis, staging, and prognosis of pancreatic neoplastic masses. In pancreatic cancer, the most used and validated serum marker of a pancreatic mass is CA 19-9 which has a reported sensitivity and specificity of 80–90%; CA19-9 is a mucinous glycoprotein normally present in glandular secretions of a mucous type. It is synthesized by pancreatic and biliary ductal cells and by gastric, colon, endometrial, and salivary epithelia. It is not found at high levels in normal tissues but can be detected at elevated levels in patients with pancreatic, hepatobiliary, gastric, hepatocellular, colorectal, and breast cancer. With a cutoff value of 37 kU/L, CA19-9 has poor sensitivity and specificity for diagnosing pancreatic cancer [51]. In the same manner, CA 19-9 is also of no value in diagnosing the malignant transformation of pancreatic cystic neoplasms [52]. However, CA19-9 levels are correlated with tumor size and small tumors may be missed; moreover, 5–10% of the population lacks the glycosyl-transferase Lewis blood group antigen required for the expression of CA 19-9 [53–55]. According to the American Society of Clinical Oncology (ASCO) guidelines, CA 19-9 should not be used as a screening marker in asymptomatic individuals due to its low-positive predictive value [56], but they recommend its use in guiding the therapeutic strategy [57]. The clinical importance of CA 19-9 is not limited only to the diagnosis; establishing serum CA 19-9 levels can provide information regarding prognosis, patient stratification (survival groups), and resectability of the disease. On multivariate analysis, preoperative CA 19-9 levels and lymph node ratio emerged as independent predictors of survival in patients with resected pancreatic ductal adenocarcinoma (PDAC) [58]. Other studies

have demonstrated that a lower value of preoperative CA 19-9 correlates with tumor resectability [59] and a better prognosis [60]. Moreover, it is useful for monitoring patients after surgery and during chemotherapy. In the case of a functioning pancreatic NEN, hormone secretion is important in determining symptoms and guiding the diagnosis. In nonfunctioning NENs, the symptoms could be absent or aspecific. Many serum markers have been proposed to guide to and sustain a diagnosis. The most important is chromogranin A (CGA) [61, 62] and, in the same way as CA 19-9, it should not be used as a screening tool for PDAC; the aforementioned markers should not be used with a screening intent but only in cases of clinical or imaging suspicion of an NEN.

1.5 Imaging: What the Clinician Should Know?

The imaging tests which best recognize pancreatic lesions include ultrasound, transabdominal (US), or endoscopic (EUS); CT, MRI, and positron emission tomography (PET), usually in combination with CT (i.e., PET-CT). As reported in Table 1.2, physicians should know what each single examination could add to defining the pancreatic mass as solid or cystic, and what they should expect from the various imaging modalities available (Fig. 1.1).

1.5.1 Transabdominal Ultrasound (US)

Ultrasound is a ubiquitous and radiation-free imaging test used worldwide, having ever-evolving applications and devices; it has the potential of displaying the pancreas, pancreatic duct, and associated lesions. The challenge with US in pancreatic disease is the structures that the US beam has to pass before it gets to the pancreas itself. Frequently, the stomach and any other bowel is filled with gas and obscures the pancreas as can excess abdominal wall adipose tissue. An experienced physician can avoid some of these pitfalls using water to distend the stomach or with varied positioning, but their use is limited. In addition, it is difficult to ensure that the entire gland was imaged on any given examination. Contrast-enhanced ultrasound has valuable diagnostic accuracy in differentiating exocrine from endocrine pancreatic tumors, a fundamental step in addressing appropriate histological evaluation, therapeutic approach, and follow-up [63]. In the case of the presence of pancreatic cystic neoplasms, three-dimensional contrast-enhanced EUS can be safely used to follow patients with IPMNs of less than 1 cm [64].

1.5.2 Computed Tomography (CT)

Computed tomography scanning is the workhorse for diagnosing pancreatic abnormalities; it provides excellent anatomic detail and does so consistently. Computed tomography scanning requires ionizing radiation, and typical pancreas protocol CT

Table 1.2 Characteristics of common pancreatic cysts

Type of cyst	Age at onset	Location	Imaging (CT/MRI)	Imaging (EUS)	Cytology	Cyst fluid analyses	Confocal endomicroscopy
IPMN (main pancreatic duct and branch-duct)	Middle-aged and older individuals	Common in the pancreatic head, may be incidental and multifocal	MD: Diffuse or focal involvement of the MPD; BD: Cyst or cluster of cysts, may be multifocal, ductal communication	MD: Dilation of the MPD, hyperechoic nodules arising from the ductal wall; BD: Small cluster of grape-like dilations of the BD, mural nodules	Colloid-like mucin, mucin stains positive, mucinous epithelial cells with varying degrees of atypia, sparsely cellular	Thick, viscous mucus, CEA concentration usually high, amylase concentration may be high, KRAS mutation	Epithelial villous structures; no vascular networking
MCN	Middle-aged women	Body and tail, incidental, single lesion	Large cysts with thick septae, peripheral calcification, wall thickening	Macrocystic lesion with few septae. Sometimes focal, peripheral, calcification. No ductal dilation. Sometimes atypical papillary projections may be present	Mucinous epithelial cells with varying degrees of atypia, colloid-like mucin, mucin stains positive	Thick, viscous mucus, CEA concentration usually high, KRAS mutation, GNAS mutation	Epithelial villous structures; no vascular networking
SCN	Usually in older women	Entire pancreas, many small cysts or oligo/macrocystic	Microcystic multiple small cysts, central fibrous scar with calcification, sometimes oligocystic	Multiple, small, anechoic cystic areas and "honeycomb" appearance, sometimes central fibrosis or calcification	Usually acellular and nondiagnostic, small cluster of cells with bland cuboidal morphology, glycogen stain positive, mucin negative	Clear and thin, may be hemorrhagic, CEA and amylase concentrations very low	Thickened cyst wall; unilocular vascular networking; fibrous bands

IPMN intraductal papillary mucinous neoplasm, *MD* main duct, *MPD* main pancreatic duct, *BD* branch duct, *MCN* mucinous cystic neoplasm, *SCN* serous cystic neoplasm, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *CEA* carcinoembryonic antigen

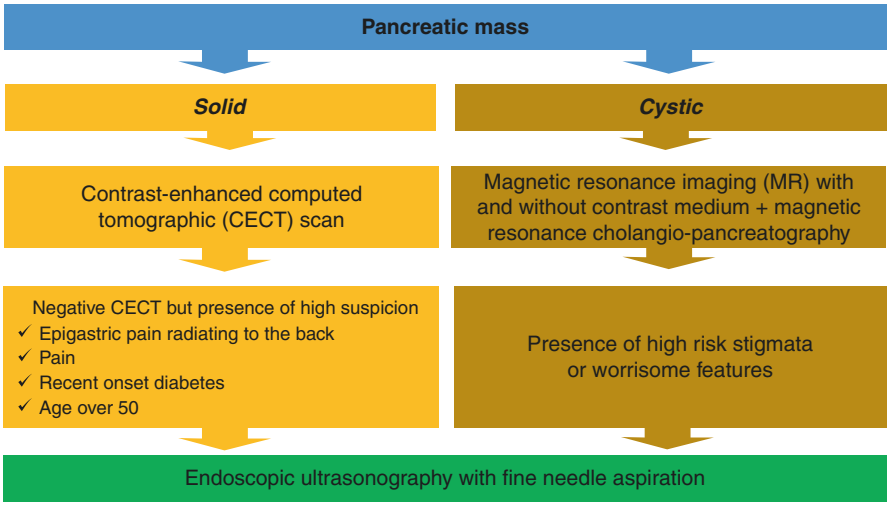

Fig. 1.1 Imaging workup for solid versus cystic pancreatic masses

scans are three-phase studies (precontrast, arterial phase, and portal venous phase imaging). In addition, iodinated intravenous contrast is required in nearly all pancreatic protocols and may be contraindicated in the setting of moderate to severe allergy or renal failure. The sensitivity and specificity of CT in diagnosing a solid pancreatic mass is high and is of paramount importance in evaluating vascular involvement; in fact, the sensitivity of CT in diagnosing vascular involvement is 98%, specificity 79%, and overall accuracy 80% having a positive predictive value of 87.5% and a negative predictive value of 96% [65].

1.5.3 Endoscopic Ultrasound and Tissue Acquisition

Endoscopic ultrasound has become the primary imaging technique for investigating patients with pancreatic lesions. Although minimally invasive, EUS does require deep sedation, and thus, patients must be appropriately evaluated with a preoperative medical assessment. It provides the option of fine-needle aspiration (FNA), and it is especially useful if the cyst morphology changes or the patient develops symptoms so that a repeat FNA can be performed. The level of carcinoembryonic antigen in the cyst fluid can be examined, and the cytological identification of lesions with a high risk of malignancy is possible. However, at present, there are limited data regarding the evaluation of molecular markers in the cystic fluid for evaluating cancer transformation. Confocal laser endomicroscopy (CLE) is a novel imaging technology which uses low-power laser to obtain in vivo histology of the gastrointestinal mucosa, and recently, a CLE miniprobe has been developed to use during EUS-FNA to visualize the cyst wall and epithelium directly through a 19-gauge FNA needle. The technical feasibility of this probe has been demonstrated, and

preliminary studies of pancreatic cystic lesions have revealed that the presence of epithelial villous structures is associated with IPMNs, having 59% sensitivity and 100% specificity [66]. Prospective studies for confirming the above are ongoing [67].

1.5.4 MRI with MR Cholangiopancreatography (MRCP)

The most comprehensive abdominal examination is MRI [68]; it offers a strong and complete pancreas examination, especially in younger patients. As opposed to CT, MRI obtains multiple complimentary sequences in addition to multiple phases of contrast enhancement. Diffusion-weighted imaging, a sequence which capitalizes on the decreased random motion of water molecules to show highly cellular tumors, is helpful in detecting otherwise occult tumors. Magnetic resonance cholangiopancreatography is useful in establishing the relationship between cystic lesions and the biliary and pancreatic ducts. However, the disadvantages of MRI are: (1) it is probably more expensive, (2) it is not universally available, and (3) it cannot be carried out in patients who have any metal implants in the body.

1.6 Treatment and Follow-Up of Patients with Solid and Cystic Lesions of the Pancreas

Solid lesions of the pancreas should be resected if the patient is fit for surgery. However, it is necessary to obtain a pathological diagnosis in order to prescribe appropriate medical therapy [69].

Cyst malignancy should be established on clinical and imaging data since a serous cystadenoma is not subject to malignant transformation [70] while an IPMN of the main duct and a mucinous cystadenoma must be removed surgically, if this is not contraindicated due to severe comorbidities. An IPMN of the secondary ducts can become malignant and, therefore, needs adequate follow-up, preferably with MRI associated with MR pancreatography or in selected cases with EUS (Fig. 1.2) [21]. The patients who should undergo EUS are therefore those with indeterminate cystic lesions, IPMNs of the secondary ducts with signs of alarm (nonspecific abdominal pain or single or recurrent episodes of acute pancreatitis not attributable to other causes, cysts of diameter ≥3 cm, main pancreatic duct dilation 5–9 mm, uptake of contrast medium of mural nodules, sudden change in the caliber of the pancreatic duct with distal pancreatic atrophy) or signs of a high risk of malignancy (obstructive jaundice, mural nodules, main pancreatic duct dilation greater than 10 mm) [21, 38]. In patients undergoing EUS, the dilemma is to decide when a sample of the cyst content is needed. The answer is when there is an unclear imaging diagnosis at CT/MRI, in inoperable patients who require chemotherapy, asymptomatic branch duct-IPMNs of 3 cm in size or with signs of a high risk of malignancy. However, MRI associated with MR pancreatography should be scheduled for monitoring pancreatic cystic lesions in branch-duct IPMNs as follows: a diameter less than 10 mm every 12 months, a diameter between 10 and 20 mm

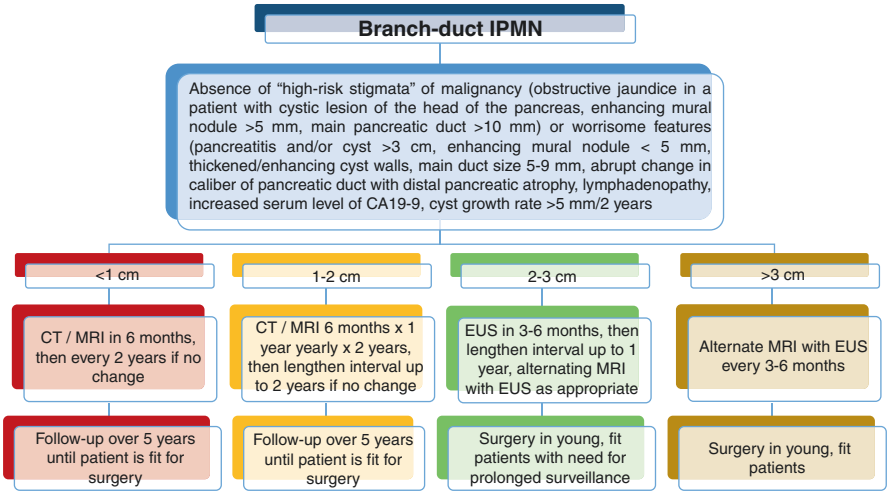

Fig. 1.2 Management of branch-duct intraductal papillary mucinous neoplasms (IPMNs). *CT* computed tomographic scan, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *CA 19-9* Carbohydrate Antigen 19-9

every 6–12 months and a diameter greater than 20 mm every 3–6 months; if the cystic lesion is stable 2 years after the initial diagnosis, the timing of the follow-up can be modified as follows: a diameter less than 10 mm every 24 months, a diameter between 10 and 20 mm every 18 months and a diameter greater than 20 mm every 12 months [71]. The question is how long should the follow-up be; whereas American guidelines recommend stopping the follow-up after 5 years if the clinical picture has not changed [72], and increasing evidence has suggested that the follow-up should be extended for more than 5 years due to the possibility of detecting malignant transformation after this period [73, 74]. The last question is the quality of life of patients followed long-term clinically and radiologically; the answer is that patients with IPMNs have a quality of life similar to the general population from both a physical and a mental point of view [19] and, thus, the long-term follow-up does not seem to affect the well-being of these subjects.

1.7 Conclusions

Clinical signs in solid tumors are important in reaching a diagnosis whereas pancreatic cysts are mainly asymptomatic, and radiological and cytological examinations are important tools in order to reach a diagnosis. In this respect, a CT scan is the optimal modality for the initial evaluation of solid pancreatic masses, including local and distant staging, and surgical planning whereas MRI/MRCP is the preferred modality for cystic pancreatic lesion assessment and can be used without contrast to follow-up incidental lesions. Endoscopic ultrasound combined with MRCP in evaluating cystic lesions is able to document the presence of carcinoma

transformation by means of an evaluation of fluid analysis and FNA of any mural nodules. Of course, in patients with cystic lesions, such as branch-duct IPMNs, who do not need immediate surgery and are fit for surgery, a medical and radiological follow-up is important to detect malignant transformation.

Conflict of Interest None to declare.

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Overview on Inflammatory Pancreatic Fluid Collection

2

Filippo Antonini and Giampiero Macarri

2.1 Introduction

Inflammatory pancreatic fluid collections (PFCs) are a varied group of collections of enzyme-rich pancreatic juice mainly collected adjacent to the pancreas and caused by a pancreatic ductal disruption [1]. They are often the result of acute pancreatitis (both interstitial than necrotizing), even if they may also be seen in chronic pancreatitis and pancreatic trauma (including abdominal surgery). A correct definition of PFCs is crucial to optimize management and treatment. Due to the large discrepancy in the way these fluid collections were previously described, in 1992 a classification on acute pancreatitis was proposed to provide consistency and uniformity of nomenclature (the Atlanta Classification) [2] and recently a revised classification was proposed [1]. According to the latter classification, PFCs are defined as acute, non-encapsulated (<4 weeks after an episode of acute pancreatitis) or chronic, encapsulated (>4 weeks after an episode of acute pancreatitis) [1]. Moreover, based on the presence of necrotic material inside the lesions, PFCs are further divided in: acute peripancreatic fluid collections (APFCs), acute necrotic collections (ANCs), pseudocysts, and walled-off necrosis (WOPNs) (Table 2.1) [1]. This chapter reviews natural history, classification, and indication of treatment of PFCs.

2.1.1 APFCs

APFCs are homogenous collections of fluid contiguous to the pancreas and are featured by the absence of a defined wall encapsulating them. They usually develop within the first 48 h of the interstitial edematous pancreatitis with no correlated

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Table 2.1 Classification system of pancreatic fluid collections in acute pancreatitis [1]

Type of acute pancreatitis	<4 weeks	>4 weeks
Interstitial edematous	*Acute peripancreatic fluid collection* – Not encapsulated – Adjacent to the pancreas (no intrapancreatic extension) – Homogeneous fluid density (no nonliquid component)	*Pancreatic pseudocyst* – Well-defined inflammatory wall (usually round or oval) – Usually peripancreatic (rare intrapancreatic extension) – Homogeneous fluid density (minimal or no necrosis)
Necrotizing	*Acute necrotic collection* – Not encapsulated – Intrapancreatic and/or peripancreatic extension – Heterogenous, non-liquified material (both fluid and necrosis) – Variably loculated	*Walled-off pancreatic necrosis* – Well-defined inflammatory wall – Intrapancreatic and/or peripancreatic extension – Heterogenous, non-liquified material (both fluid and necrosis) – Variably loculated

peripancreatic necrosis. In the first days of acute pancreatitis, a clear differentiation between APFCs and ANCs could be difficult because both can present as non-enhancing areas at CT scan. Most of them remain asymptomatic, sterile, and resolve spontaneously within 2–4 weeks in 50% of patients [3]. Acute collections usually do not require any interventional treatment. Rarely, they can persist and evolve into pseudocyst (<10% of cases) [4].

2.1.2 ANCs

ACNs develop from pancreatic glandular or peripancreatic fatty tissue necrosis in case of acute necrotizing pancreatitis. Within the first weeks of onset of the acute necrotizing pancreatitis, any apparent collection that replaces or occupies pancreatic parenchyma should be considered an ANC. In the 75–80% of cases, they are both pancreatic and peripancreatic [5]. They lack a definable wall, and necrotic content may be sterile or infected. In contrast to APFCs that resolve spontaneously and only a minority transform into pseudocyst, a considerable amount of ANCs transform into WONs [6, 7].

2.1.3 Pancreatic Pseudocysts

Pseudocysts are described as well-circumscribed encapsulated collections of fluid surrounded by nonepithelial wall of fibrous or granulation tissue that is commonly outside the pancreas that does not have any necrotic material [1]. Pancreatic pseudocysts usually occur more than 4 weeks after the onset of interstitial edematous pancreatitis. The presence of pseudocysts ranges from 5% to 16% in acute

pancreatitis, and 20% to 40% in chronic pancreatitis. Alcohol is the etiological agent in most (64%) of chronic pancreatitis patients, whereas gallstone disease was the cause for 26% of acute and for 11% of chronic pancreatitis patients. Differential diagnosis from pancreatic cystic neoplasms is mandatory to avoid unnecessary pancreatic surgery and ensure patients excluding a malignant disease [8]. On the other hand, it was found that as many as 37% of pancreatic cystic neoplasms were misdiagnosed as pseudocysts and it was even confirmed as malignant lesions after surgery. Although knowing previous history of pancreatitis could be useful in distinguishing pancreatic pseudocysts from cystic neoplasms, clinical, and radiological characteristics must be considered for differentiate these lesions. The choice of appropriate imaging modality depends on the reason for investigation, clinical scenario, and time of onset of symptoms. Contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) are extremely sensitive and can help recognize these lesions in 88% to 94% of cases [9, 10]. Pancreatic pseudocysts appear usually as a round or oval collections, typically extrapancreatic, with a well-defined wall, with homogeneous fluid density, containing no non-liquefied components or internal septae. MRI allows better distinction between solid necrotic and predominantly fluid collections [11]. On MRI, the presence of internal dependent debris appears to be a highly specific finding for the diagnosis of pancreatic pseudocyst. Moreover, magnetic resonance cholangiopancreatography (MRCP) can give relevant information about pancreatic parenchyma and pancreatic ductal integrity [12]. When morphologic features reported by radiological imaging techniques are insufficient to differentiate cystic lesions, endoscopic ultrasound (EUS) can provide further, additional and useful information [13]. Indeed, EUS provides high-resolution images over a short distance to the pancreas, accurately showing every cystic element as well as detailed images of the parenchyma [14]. EUS is also mandatory when an endoscopic treatment is required.

Most pancreatic pseudocysts are asymptomatic and endure spontaneous resolution. In the past, some studies suggested that large pseudocysts that persist for more than 6 weeks are likely to generate symptoms and should be treated [15]. However, new evidence suggests that pseudocysts can remain asymptomatic regardless of size or duration and that spontaneous resolution happens most of the time (varying from 7% to 60% of patients) [16]. For this reason, pseudocysts that occur with acute pancreatitis should be maintained under observation, and the treatment should be reserved only for those patients who develop symptoms [17, 18]. Symptomatic patients can present abdominal pain, precocious satiety, weight loss, and vomiting. Other symptoms may be the infection of the pseudocyst, gastric outlet obstruction, and biliary obstruction [19]. Erosion of the pseudocyst into attached vessels may also bring to a pseudoaneurysm formation and/or hemorrhage that could be life-threatening. Finally, decisions should be made in a multidisciplinary setting based on the patient's condition, etiology, symptoms, and clinical history (Fig. 2.1).

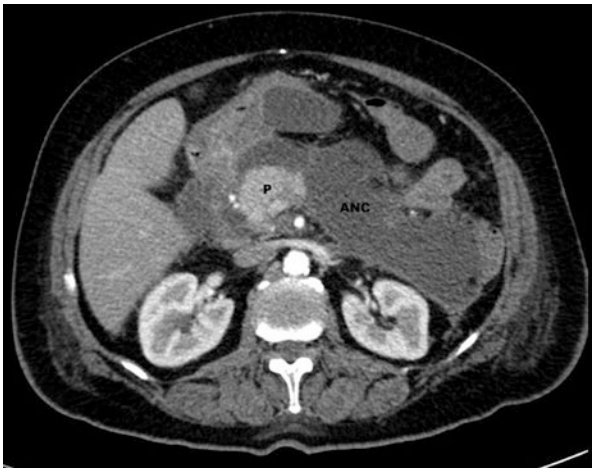

Fig. 2.1 Contrast-enhanced (CT) image 4 days after the onset of acute pancreatitis: acute necrotic collection (ANC) of the pancreatic body and tail, with normal parenchyma of the head (P)

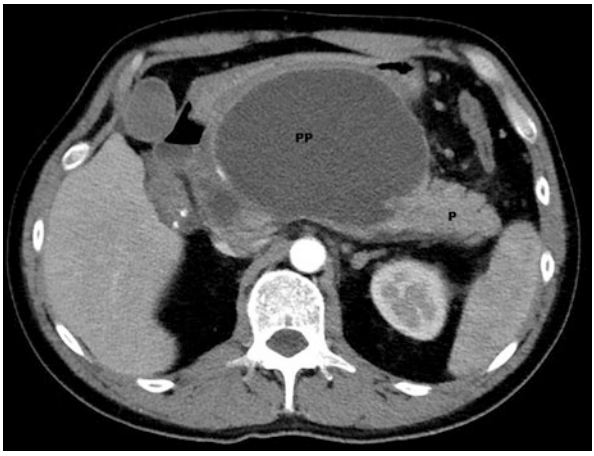

Fig. 2.2 Contrast-enhanced (CT) image 5 weeks after the onset of acute pancreatitis: large pancreatic pseudocyst (PP) of the pancreatic body, with normal parenchyma of the tail (P)

2.1.4 WONs

WONs are defined as mature, encapsulated collections of pancreatic or peripancreatic necrosis that are surrounded by an encapsulating wall. They amount to less than 5% of PFCs. These lesions evolve from ANCs over time and usually develop more than 4 weeks after an episode of necrotizing acute pancreatitis. As ANCs, even WON can affect areas of pancreatic parenchyma only, peripancreatic tissues only or, most commonly, both [1]. For these reasons, sometimes WON can still be seen at sites distant from the pancreas (Fig. 2.2).

Differential diagnosis with pseudocysts is facilitated by the presence of necrosis (solid component) within the collection [12]. CT scan is not always able to detect the solid component inside the collection and thus WON may be sometimes misdiagnosed as a pseudocyst [11]. In these cases, transabdominal ultrasound, MRI,

or EUS may be useful to identify the presence of necrosis. Moreover, extension to paracolic space, irregular wall definition, and pancreatic deformity or discontinuity could be associated with WOPN. On the other hand, the presence of pancreatic ductal dilation was connected with pancreatic pseudocyst. WON and, less frequently, the other collections can be sterile or infected. The presence of extraluminal gas within the collection is pathognomonic of infected collection, and percutaneous or EUS-guided fine-needle aspiration (FNA) is not recommended in these patients [18]. However, since in patients with infected necrosis gas formations occur in only about half of the cases [20, 21], where infection is suspected and clinical/imaging signs are unclear, FNA should be performed to guide antimicrobial-targeted therapy [18]. In the absence of clear imaging characteristics, the presence of WON should be suspected in case of protracted clinical course or severe clinical deterioration despite optimal supportive care.

The distinction between WON and pancreatic pseudocyst is of crucial importance, because the management is completely different. In both cases only symptomatic patients should be treated, but pancreatic pseudocyst requires management of pain or size-related symptoms whereas WON requires necrosectomy with debridement of solid internal components [22]. Until a few years ago, surgical debridement was the gold standard for treatment of WONs [23, 24]. More recently, less-invasive approaches have been proposed as the optimal treatment, since some studies demonstrated that a minimally invasive step-up approach decreased mortality and complications when compared to open necrosectomy [25]. Percutaneous drainage under radiological guidance has been introduced with good results, but the inability to reach complete solid debris can led to surgical rescue in about 40% of patients with WON [26–28]. Compared with open surgery, percutaneous drainage could effectively reduce the average hospital length of stay and hospital cost and avoid surgically related complications [29]. In the last few years, direct transgastric endoscopic debridement has emerged as a very promising technique in patients with WONs [30, 31]. In the endoscopic approach, a fistula with stomach (cystogastrostomy) or duodenum (cystoduodenostomy) is created by using transluminal access. At the beginning, endoscopic drainage was performed in patients with pseudocysts by directly puncturing a visible "bulge" under traditional endoscopic vision [32, 33]. More recently, EUS has been used to perform the procedure under endosonographic vision (even in the absence of compression), with the advantage to decide the best site of puncture and thus avoid vessels and other viscera [34]. EUS-guided drainage of PFCs is associated with higher technical success (95% vs 35–66%) and lower adverse event rates (0–4% vs 13–15%) than conventional direct puncture technique [35, 36]. After the puncture of pancreatic collection, fluid aspiration can be performed to obtain culture which can be used to start antibiotic therapy. Several stents can be used to recover in maturation of fistulous tract [37]. If the cyst fluid is thick and contains solid debris, as in case of WON, the endoscopist should put metallic large-bore stents and then perform direct necrosectomy by driving a front viewing endoscope with subsequent removal of necrotic debris by using tools such as snares, baskets, and water jets. Hydrogen peroxide is used to liquefy the debris

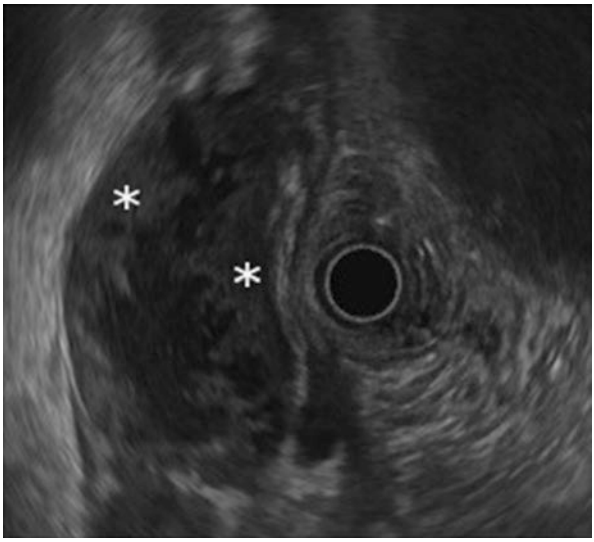

Fig. 2.3 Endoscopic ultrasound (EUS) image 4 weeks after the onset of acute pancreatitis: a pancreatic walled-off necrosis with liquid and solid (asterisks) contents

which can then be eliminated through a series of procedures. Nasocystic tubes can be also used to wash the cystic cavity for multiple days depending on the patients need and the amount of debris present [38] (Fig. 2.3).

2.2 Conclusions

PFCs include a variety of inflammatory fluid collections named separately and classified according to the time course (≤4 weeks or >4 weeks from *onset* of acute pancreatitis) and to the presence or absence of necrosis within the cavity. Each collection can be sterile or infected. These lesions are associated with increased morbidity and mortality, especially in patients with necrotizing acute pancreatitis. Differential diagnosis is crucial to assess the best management even if a clear distinction between pancreatic cysts is sometimes difficult to make. Indeed, not all cysts discovered during an episode of acute pancreatitis are inflammatory. It must be remembered that cystic neoplasms can sometimes cause acute pancreatitis, or patients with acute pancreatitis may harbor incidental cystic neoplasms. Imaging features, clinical presentation, and follow-up are important to make this differentiation.

The management of PFCs has evolved with time. The vast majority of acute PFCs (ANCs and APFCs) and most pancreatic pseudocysts do not require any intervention as they normally undergo resolution with conservative management (nutritional support, fluid resuscitation, antibiotics when needed). Nevertheless, any kind of interventional treatment within first few weeks should be avoided as much as possible because it is associated with worse outcomes and must be reserved for patients with acute pancreatitis and infected necrosis with clinical deterioration. In absence of symptoms, size alone does not necessitate treatment. Whenever possible,

the general recommendation is to wait until at least 4 weeks after initial presentation to allow the collection to become "walled-off," and to address interventional treatment only for symptomatic patients. The options of drainage for PFCs include surgery, percutaneous radiological drainage, and endoscopic transmural drainage. While symptomatic pancreatic pseudocysts can be managed by endoscopic or radiological internal drainage alone, in case of WONs a formal necrosectomy with removal of necrosis within the cavity is needed. In the last years, new endoscopic techniques and devices have emerged to improve the efficacy and safety of drainage/debridement of PFCs, thus reserving surgical approach only in a small number of patients. Nowadays, EUS-guided drainage is advised to be the best choice for the majority of patients. Anyway, a multidisciplinary and expert team including gastroenterologists, therapeutic biliopancreatic endoscopists, surgeons, interventional radiologists, and specialists in critical care medicine is needed to correctly manage patients with PFCs and to minimize morbidity and mortality related to these collections.

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3 Contrast-Enhanced Endoscopic Ultrasound and Endoscopic Ultrasound Elastography

Anna Cominardi and Pietro Fusaroli

3.1 Introduction

A precise characterization and an accurate differential diagnosis of pancreatic lesions are of utmost importance in order to accomplish the better clinical and therapeutic strategy for the patient.

Since its first introduction in 1980, endoscopic ultrasound (EUS) has become an important diagnostic technique for the evaluation of both solid and cystic pancreatic masses and their relationship with adjacent anatomic structures and blood vessels in order to distinguish their benign or malignant nature.

Nevertheless, even considering EUS high diagnostic accuracy, the differential diagnosis of pancreatic lesions still remains a challenge.

This gap has been bridged by the development of ancillary techniques, such as contrast-enhanced harmonic EUS (CH-EUS) and EUS elastography (EUS-E). The aim of this chapter is to describe these two innovative techniques.

3.2 Contrast-Enhanced Harmonic Endoscopic Ultrasound (CH-EUS)

The employment of an intravenous contrast agent for the study of the pancreatic masses was first described in 1995 by Kato et al. [1]. They inserted a catheter in the superior mesenteric artery or coeliac artery to inject carbon dioxide, which allowed the visualization of vascularization by EUS. The limit of this technique was the necessary application of angiography during EUS examination.

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This limitation was overcome by the development of new types of ultrasound contrast agents, namely "first-generation agents" such as Levovist, and the advent of color and power Doppler.

Although, color and power Doppler facilitate the visualization of blood vessels, these diagnostic techniques allow the detection only of larger vessels and they are subject to multiple tissue artifacts, such as blooming or tissue motion.

In 2005, second-generation contrast agents were used for the first time; they consist in microbubbles of inert gases covered by phospholipids, polymers, surfactant, or albumin. These are SonoVue (sulfur hexafluoride, Bracco Imaging, Italy), Sonazoid (perfluorobutane, GE Healthcare, USA), Definity (octafluoropropane, Lantheus Medical Imaging, USA).

The detection of these microbubbles in smaller vessels avoiding Doppler-related artifacts was achieved with the development of harmonic technology. Harmonic technology relies on the physic principle that tissue is almost incompressible, unlike microbubbles of the contrast agent, which can be compressed by the ultrasound beam. Particularly, the transducer generates ultrasound waves that alter the normal oscillations of the microbubbles into blood vessels. As a result, microbubbles compression and expansion is produced generating a large amount of harmonic signals. Contrast-enhanced harmonic EUS selectively depicts this harmonic component generated by microbubbles (whose harmonic content is higher than that of the surrounding tissue) and, thus, allows the visualization of smaller vessels with slow flow, not detectable by Doppler imaging [2].

3.2.1 CH-EUS: How to Do It?

The reconstituted vial of contrast agent is injected into a peripheric vein followed by 5–10 mL of saline. The effects are usually seen 10 s after infusion, with a maximum peak after 20–30 s [2]. Contrast agent lasts about 60–90 s depending on cardiac frequency, pulse length, distance between lesion and transducer, type of contrast, and imaging parameters.

The insonation energy from the transmitted ultrasound wave transducer is expressed by the mechanical index (MI), which should be set to 0.2–0.4 [3].

At CH-EUS normal pancreatic parenchyma shows a homogeneous enhancement, while the bile duct and the pancreatic duct remain non-enhanced. CH-EUS plays a crucial role in the differential diagnosis of pancreatic masses, especially for the differentiation between benign and malignant lesions.

3.2.2 CH-EUS Features of Solid Pancreatic Masses

3.2.2.1 Pancreatic Intraepithelial Neoplasia (PanIN)

PanIN represents the precursor of pancreatic adenocarcinoma, and while PanIN-1 and 2 are not detectable with endoscopic ultrasound, PanIN-3 is described as a hyper-enhanced lesion at CH-EUS [4].

3.2.2.2 Pancreatic Adenocarcinoma

CH-EUS showed a pooled sensitivity of 93–94% and specificity of 88–89% in the differential diagnosis of pancreatic adenocarcinoma [5, 6].

Pancreatic adenocarcinoma usually shows an inhomogeneous hypo-enhanced aspect with an irregular arterial architecture and disappearance of veins. This poor vascularization generates a rapid washout during CH-EUS [7]. However, iso- or hyper-enhanced pancreatic adenocarcinoma is rarely encountered (Fig. 3.1).

3.2.2.3 Neuroendocrine Tumor (NET)

Although NETs show a hypo-echoic aspect during EUS, they appear hyper-enhanced on CH-EUS as a result of their rich arterial vascularization (Fig. 3.2).

3.2.2.4 Solid Pseudopapillary Tumor (SPN)

SPNs are characterized by inhomogeneous enhancement of the thickened peripheral capsule and solid components surrounding the cystic and necrotic avascular areas [8, 9].

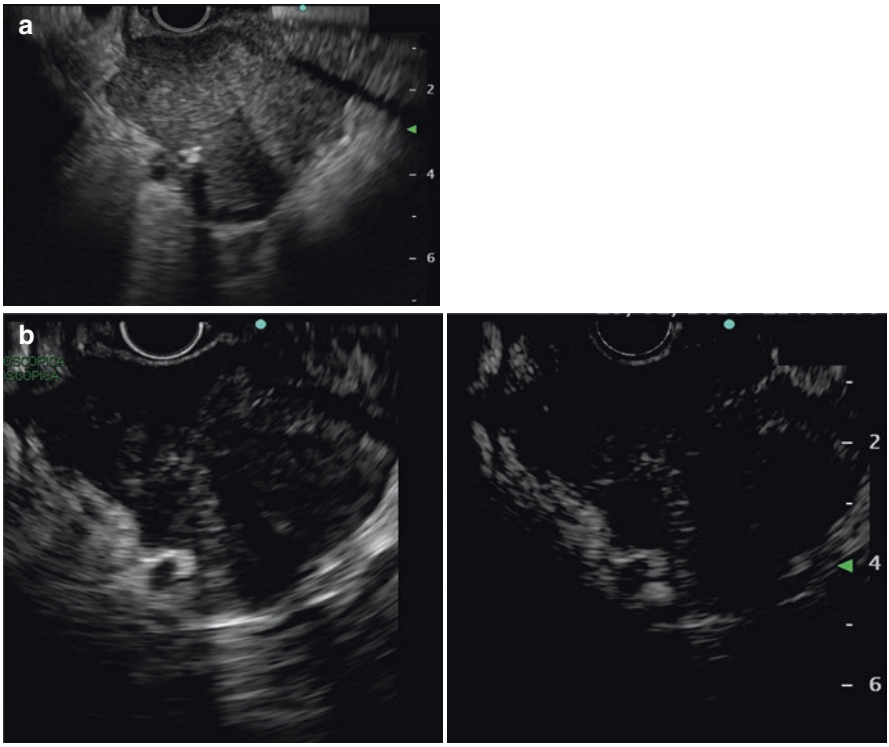

Fig. 3.1 Pancreatic body adenocarcinoma. The lesion was firstly evaluated by EUS, which showed a hypo-echoic lesion in the body of pancreas (**a**). Subsequently, the lesion was investigated with contrast harmonic after injection of the contrast agent. In the arterial (**b**) and venous (**c**) phase, the lesion appeared hypo-enhanced. Lastly, EUS-E showed a homogenous blue pattern (**d**)

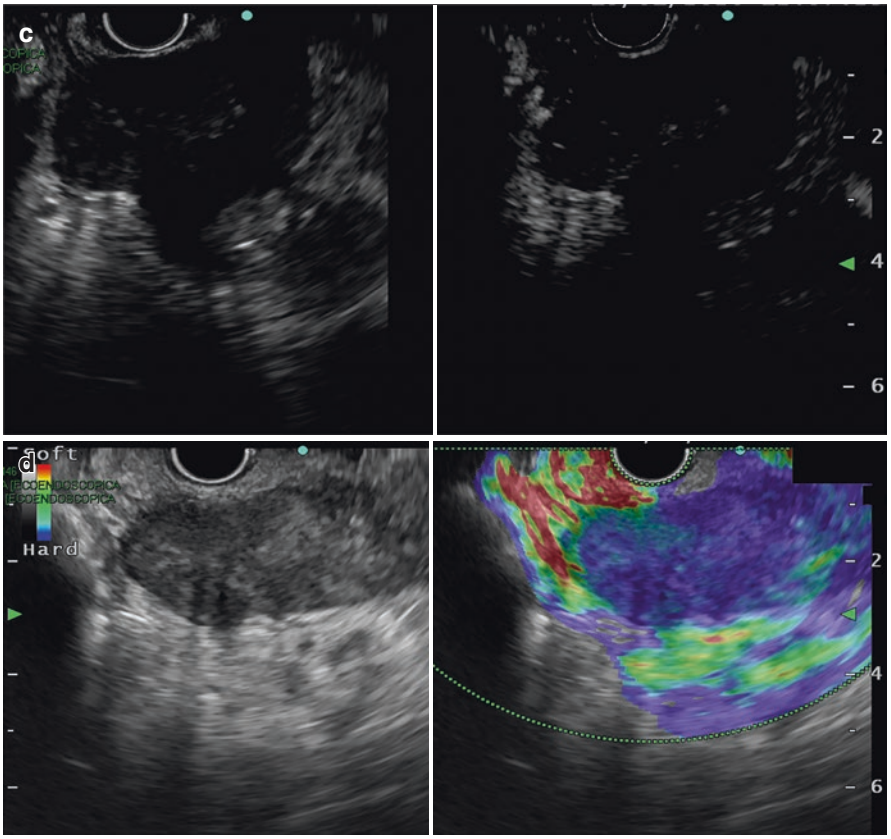

Fig. 3.1 (continued)

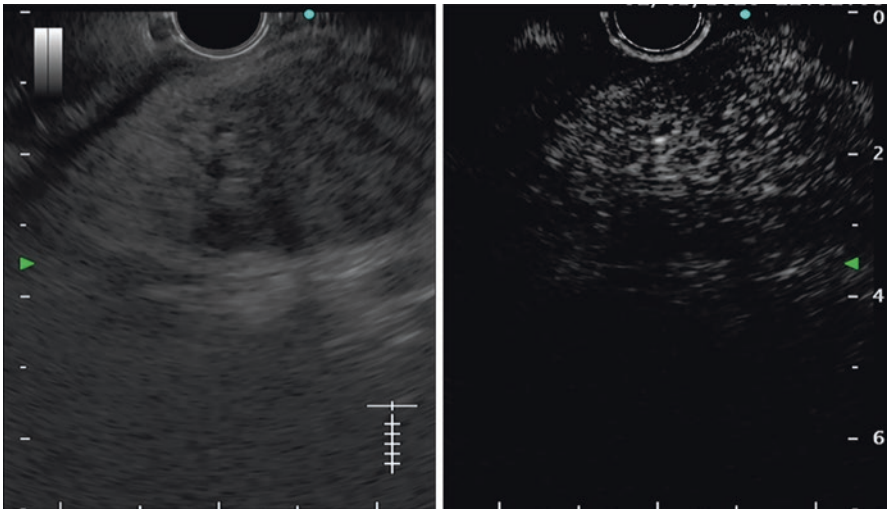

Fig. 3.2 CH-EUS of a neuroendocrine tumor that appeared hyper-enhanced

3.2.2.5 Metastases

Pancreatic metastases are usually characterized by rapid washout. The most common primary tumors are breast, renal, and colon neoplasm. Metastases usually show inhomogeneous hypo-enhanced pattern; however, lymphoma and renal cancer had been shown to have hyper-enhanced and homogenous pattern [10, 11].

3.2.2.6 Acute Pancreatitis

The employment of contrast-agent in the EUS examination of acute pancreatitis allows the early visualization of necrotic areas, which appear non-enhanced. This is useful especially for patients with renal failure because CT contrast agent is contraindicated for them.

3.2.2.7 Chronic Pancreatitis

Focal chronic pancreatitis usually appears hypo-enhanced with regular microvascular architecture. The analysis of arterial and venous vascular pattern is essential for the differentiation between pancreatitis and adenocarcinoma. Focal pancreatitis is characterized by homogenous vascular pattern with both arterial and venous vessel depicted; on the other hand, pancreatic adenocarcinoma shows an irregular vessels system without venous component displayed [4].

3.2.2.8 Autoimmune Pancreatitis

CH-EUS helps for the differentiation of the typically hypo-enhanced adenocarcinoma from autoimmune pancreatitis, which is usually iso-enhanced in the arterial phase and hyper- or iso-enhanced in the late phase [12] (Fig. 3.3).

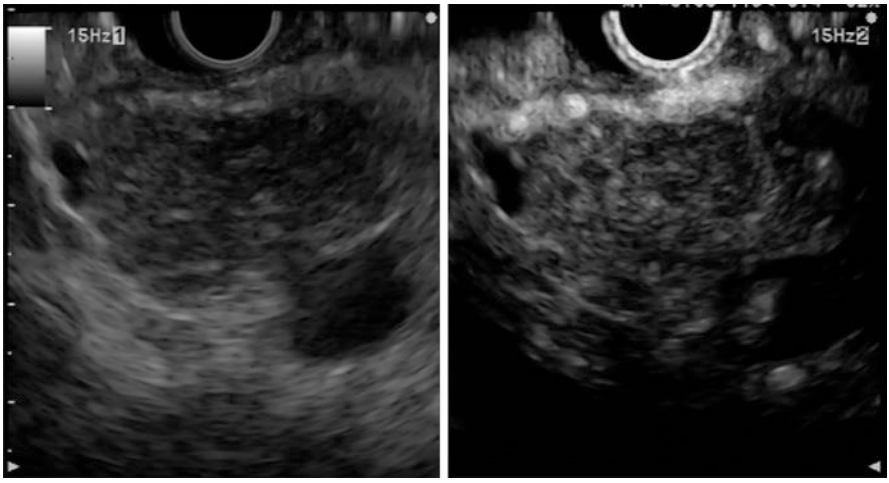

Fig. 3.3 CH-EUS of autoimmune pancreatitis. The lesion appeared iso-enhanced compared to the surrounding pancreatic parenchyma

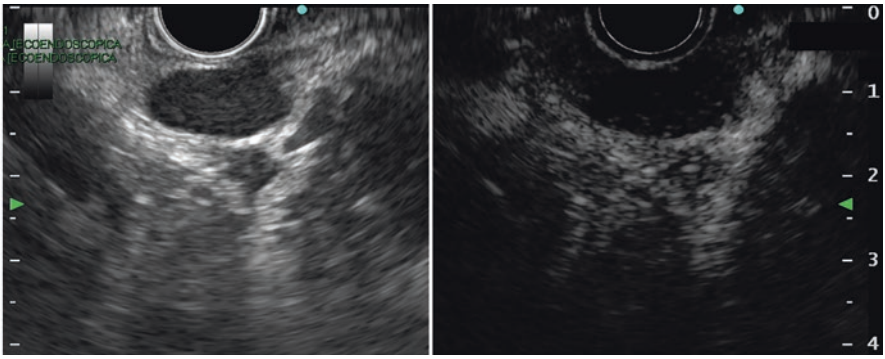

Fig. 3.4 CH-EUS showed a hypo-enhanced lymph node near the pancreas, which was suggestive of a possible malignancy

3.2.2.9 Lymph Nodes

Malignant lymph nodes are usually characterized by destroyed vascular system without hilar vessels. Areas with patchy or missing contrast-enhancement could be often observed [13] (Fig. 3.4).

3.2.2.10 Lymphoma

Primary pancreatic lymphoma is a rare tumor and little is known about its CH-EUS aspect. It has been described to have a hypo-enhancing pattern [14], although pancreatic metastases of lymphoma have been described as hyper-enhancing [15].

3.2.2.11 Pancreatoblastoma

Little is known about this high-grade malignancy tumor. It was described to appear hypo-enhanced in the arterial phase and iso-enhanced in the venous phase [16].

3.2.2.12 Schwannoma

It usually presents a hyper-enhancement pattern, although it does not show a pathognomonic pattern.

3.2.2.13 Lipoma

At CH-EUS, lipomas usually appear hypo-enhancing [17].

3.2.2.14 Perivascular Epithelioid Cell Tumor (PEComa)

PEComa is a mesenchymal cell neoplasm and rarely it grows in pancreatic parenchyma. In a recent study, it showed a long-lasting hyper-perfusion with late "washout" during CH-EUS [18].

The enhancing features of the main pancreatic solid lesions are summarized in Table 3.1.

Table 3.1 Contrast-enhancing characteristics of solid pancreatic lesions

Pancreatic lesion	CH-EUS
Pancreatic adenocarcinoma	Generally inhomogeneous hypo-enhancement with rapid washout Irregular arterial architecture without venous vascularization
Neuroendocrine tumor	Hyper-enhanced
Necrotic acute pancreatitis	Non-enhancing of necrotic areas
Chronic pancreatitis	Hypo-enhanced with regular arterial and venous architecture
Autoimmune pancreatitis	Early iso-enhancing and late hyper- or iso-enhancing
Malignant lymph nodes	Patchy or missing enhancement

3.2.3 CH-EUS Features of Cystic Pancreatic Masses

3.2.3.1 Simple Pancreatic Cysts and Pseudocysts

CH-EUS evaluation of a cystic lesion is important in order to differentiate malignant from benign cysts; the presence of wall or nodule vascularization, and consequently enhancing, is suggestive for malignant cystic lesion [19].

Pseudocysts usually appear as hypo-enhanced during all phases because they usually contain avascular material; some vessels could be found within the cyst only on early stages [4].

3.2.3.2 Intraductal Papillary Neoplasms (IPMN)

CH-EUS has been demonstrated to play an important role in the differential diagnosis between malignant and benign IPMNs through the differentiation of perfused (nodules) and non-perfused areas (mucus clots) [4]. Malignant IPMNs could be suspected according to the enhancing pattern of mural nodules indeed, and invasive IPMNs are characterized by hyper-enhanced papillary and invasive nodules [20] (Fig. 3.5).

3.2.3.3 Mucinous Cystic Neoplasms (Cystadenoma and Cystadenocarcinoma)

They could appear at CH-EUS examination as cystic lesions with intralesional irregular septation and parietal nodule enhancement.

3.2.3.4 Serous Cystadenoma

It shows intralesional irregular septation enhancement and hyper-enhanced parietal nodule [9]. It should be underlined that CH-EUS cannot distinguish between serous and mucinous cystic lesions because their septa and parietal nodules have similar enhancement (Fig. 3.6).

3.2.4 CH-EUS-Guided Tissue Sampling

The definitive diagnosis of pancreatic lesions usually results from the pathologic examination of tissue samples from the lesion, which can be obtained by

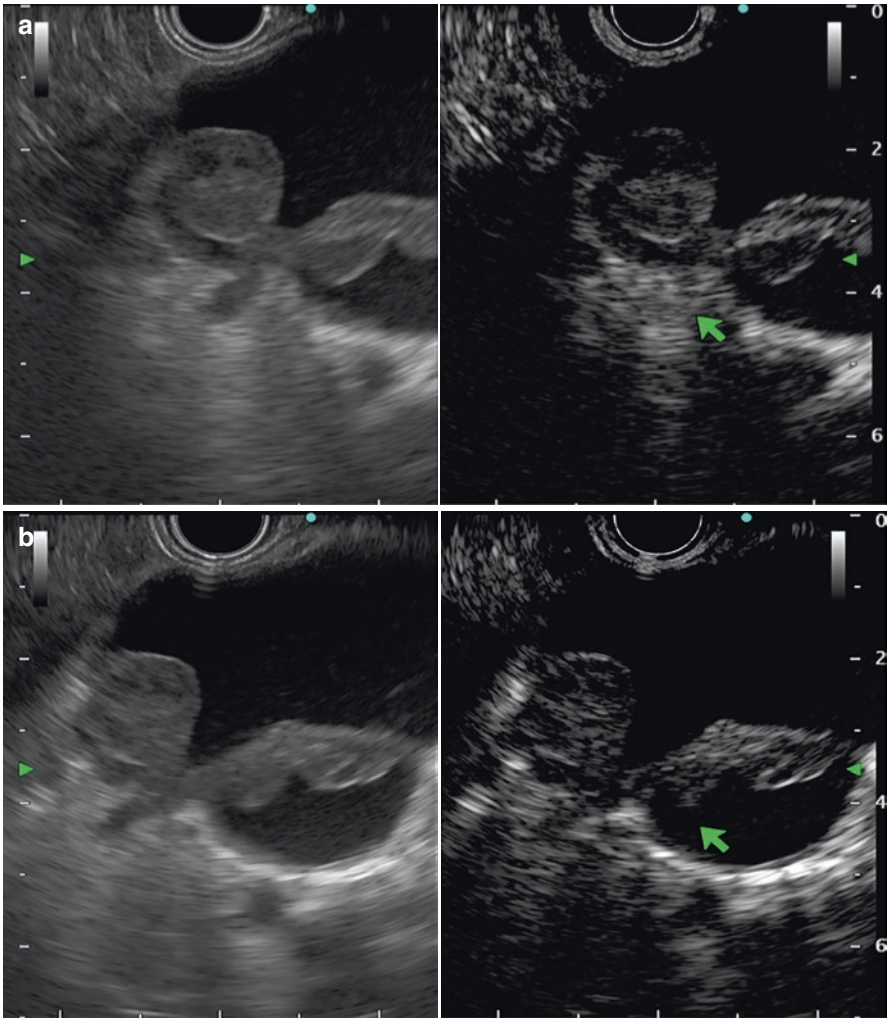

Fig. 3.5 CH-EUS of a branch-duct intraductal papillary mucinous neoplasm. In the arterial phase, (**a**) the septa and nodule showed hyper-enhancement. In the venous phase, (**b**) the nodule showed a slow washout. These features were suggestive for malignancy arising in the nodule itself

EUS-guided fine-needle aspiration (EUS-FNA) or EUS-guided fine-needle biopsy (EUS-FNB).

The employment of the contrast agent during EUS not only allows a better characterization of the pancreatic lesions but also may be useful as a guidance for a more precise tissue sampling.

The identification of the better target area to sample, in fact, reduces the possibility of false-negative results or uncertain diagnosis and, consequently, decreases repeated EUS-FNA procedures.

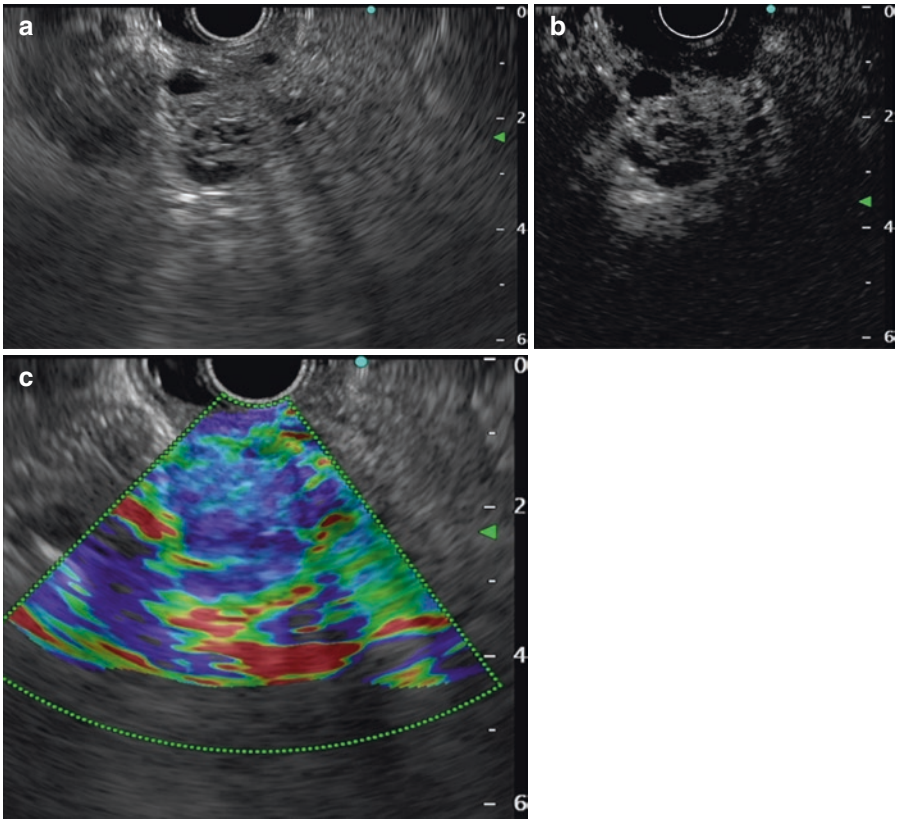

Fig. 3.6 A serous cystadenoma showing a classical honeycomb pattern (**a**). CH-EUS (**b**) showed diffuse hyper-enhancing of the septa and pseudo-solid components. At EUS-E, (**c**) the lesion appeared stiffer than the normal pancreatic parenchyma

EUS-FNA accuracy is generally lower in presence of avascular areas that are characteristic of ductal pancreatic adenocarcinoma. The employment of CH-EUS for EUS-FNA or FNB helps in avoiding these areas, which usually appear as non-enhancing. In detail, the diagnostic sensitivity for pancreatic adenocarcinoma was shown to be risen from 92% to 100% when EUS-FNA evaluation was combined with CH-EUS [21]; however, the sensitivity remained low for carcinomas with avascular areas on CH-EUS [22]. Thus, if EUS-FNA results inadequate for pathologic diagnosis of a pancreatic lesion characterized by an avascular area on CH-EUS, then alternative diagnostic methods should be considered (pancreatic juice cytology or biopsy sampling of liver metastases) [22].

3.3 Endoscopic Ultrasound Elastography (EUS-E)

Elastography represents another valuable methodic that could help in the differential diagnosis of pancreatic lesions.

The term “elastography” and the related studies about different tissue elasticity and its measurement were introduced in late 1980s [23], but only in 2001 they were applied to B-mode imaging [24].

It lays on the principle that an inflammatory or neoplastic process generates a change in tissue structure and consequently, in its elasticity, making it softer or harder.

Two types of elastography techniques are currently available: strain and shear wave elastography; the former measures tissue stiffness through the evaluation of tissue distortion after applying pressure, while the latter, after applying acoustic radial force impulse [25]. Only strain elastography has been extensively studied for EUS applications so far.

EUS strain elastography represents a qualitative method for the measurement of tissue deformation (strain) within a region of interest (ROI), and it is visualized using a transparent color overlay on the B-mode image [26]. According to strain elastography color scale, harder tissues appear as blue areas while softer tissues look red; finally, green and yellow depict areas with intermediate elasticity.

3.3.1 EUS-E: How to Do It?

The lesion of interest should occupy 25–50% of the region of interest (ROI), and a sufficient quantity of normal reference tissue should be also included within the same ROI.

After the individuation of the best scanning position, the first ROI should be positioned in correspondence of the target lesion area and a second ROI should be placed above normal tissue. Thus, it is possible to quantify the mean strain of these areas and the strain ratio, which is the quantification of the difference between the two areas in terms of strain.

Vessels and fast-moving organs, such as pleura, bowel wall, and peritoneum, should not be included within ROI because their physiological movements create artifacts during EUS-E. Normal pancreatic parenchyma is usually isoechoic to normal liver parenchyma, and it shows an intermediate stiffness (it usually appears green at EUS-E); its stiffness increases with age, but it is not affected by body mass index, weight, and gender [23].

3.3.2 EUS-E Features of Solid Pancreatic Masses

3.3.2.1 Pancreatic Adenocarcinoma

Neoplastic transformation is characterized by many desmoplastic reactions and increase of extracellular matrix that make tissue harder than surrounding parenchyma. Therefore, pancreatic adenocarcinoma usually appears blue at EUS-E.

3.3.2.2 Neuroendocrine Tumor

Initially, pancreatic NET was shown to be stiffer than the normal pancreatic parenchyma, so it usually had a homogenous or inhomogeneous blue elastography pattern [27, 28]. However, subsequent studies showed that up to two-thirds of pancreatic NETs are usually green as they are softer than surrounding parenchyma [29]. In a recent study, EUS-E was showed to ruled out malignancies with a high level of certainty if the lesion appears soft (like NETs), while a stiff lesion can be either malignant or benign [29].

Recently, fractal analysis-based technology (the estimation of complexity in shape of a biologic tissue, its roughness, or its underlying nonlinear dynamic behaviors) was applied to elastographic images, and it showed that the surface fractal dimension of malignant pancreatic lesions was significantly different when compared with that of NET or benign lesions, and a statistical difference for all three channels red, green, and blue was also described [30]. Thus, a combination of EUS-E with fractal analysis and Red-Green-Blue (RGB) color-based computer-aided image analysis was shown to be an effective tool for differential diagnosis of pancreatic lesions [30] (Fig. 3.7).

3.3.2.3 Solid Pseudopapillary Tumor

Little is known about endoscopic ultrasound elastography of solid pseudopapillary neoplasms; in one study, one case of SPN showed a strain ratio similar to that of pancreatic cancer and pancreatic metastasis [31].

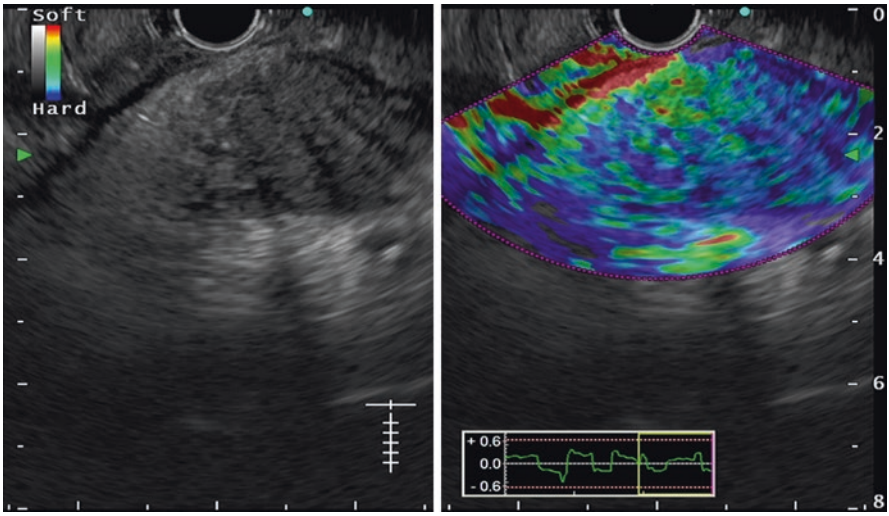

Fig. 3.7 EUS-E of a neuroendocrine tumor. The lesion appeared stiffer (blue-colored) compared to the surrounding pancreatic tissue

3.3.2.4 Metastases

Pancreatic metastases usually are stiffer than surrounding tissue. During EUS-E, they appear as circumscribed blue areas. A central green region can sometimes be found corresponding to a hypervascular areas that sometimes characterize small pancreatic metastases [32].

3.3.2.5 Acute Pancreatitis

EUS-E does not show pathognomonic aspect of acute pancreatitis because this inflammatory process induces many changes in pancreatic parenchyma with no clear-cut stiffness values [33]. Necrotic areas within acute pancreatitis are softer than normal pancreatic tissue.

3.3.2.6 Chronic Pancreatitis

Early stages of chronic pancreatitis could show a honeycombed stiffness pattern with stiff strand and calcifications [28]. This chronic process is characterized by fibrotic areas that increase both tissue stiffness and strain ratio during EUS-E. Moreover, correlation between strain ratio and fibrosis score and EUS scoring system (Rosemont criteria) was demonstrated [23]. Higher strain ratio was also observed in patients with chronic pancreatitis associated to pancreatic enzyme insufficiency [34].

3.3.2.7 Autoimmune Pancreatitis

The whole pancreatic parenchyma becomes stiffer and hypervascularized in case of autoimmune pancreatitis, appearing blue during EUS-E [35]. This elastographic pattern helps the differential diagnosis between autoimmune pancreatitis and pancreatic adenocarcinoma, because, although they both appear as blue-areas, the former involves large areas of the organ, while the latter is circumscribed [28] (Fig. 3.8).

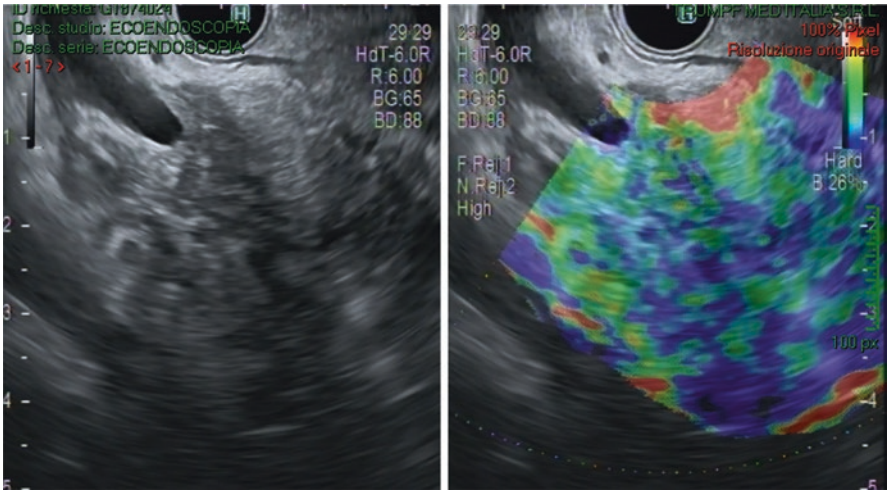

Fig. 3.8 EUS-E of autoimmune pancreatitis showed a heterogeneous green-blue-colored pattern, unlike pancreatic adenocarcinoma that has a prevalent blue component

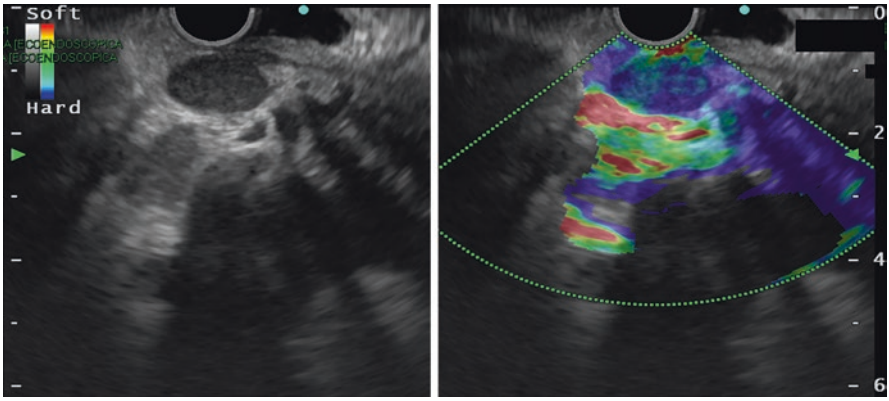

Fig. 3.9 EUS-E of a malignant lymph node, which showed a predominant blue pattern

3.3.2.8 Lymph Nodes

EUS-E helps in the differentiation between malignant and benign lymph nodes because. When they are infiltrated by neoplastic cells, lymph nodes usually become stiffer and gain a blue-colored pattern (Fig. 3.9).

3.3.3 EUS-E Features of Cystic Pancreatic Masses

Few studies about EUS-E of cystic pancreatic lesions are available.

In theory, elastography could be useful in the differentiation between malignant and benign nodules or septa within cysts. Malignant component of cystic lesions present stiffer (blue) tissue than normal pancreatic tissue (Fig. 3.10).

3.3.4 EUS-E-Guided Tissue Sampling

Although EUS-guided tissue sampling is the gold standard for the diagnosis of pancreatic lesions with high specificity (up to 100%), it has a variable sensitivity, ranging from 85% to over 93%.

In particular, EUS-FNA sensitivity is only 54% to 74% for solid pancreatic masses in the setting of chronic pancreatitis [36], thus leading to false-negative results.

The risk of negative or nondiagnostic samples can be reduced by the employment of EUS-E: this technology allows the individuation of the harder area of a lesion (more likely to be malignant) in order to precisely target tissue-sampling. It was shown that the sensitivity of the combination of EUS-E and tissue sampling rose to 93% with a diagnostic accuracy and specificity of 94% and 100%, respectively [37].

Furthermore, EUS-E may help in the differentiation between malignant and benign lesion on the basis of different tissue elasticity, proving to be useful

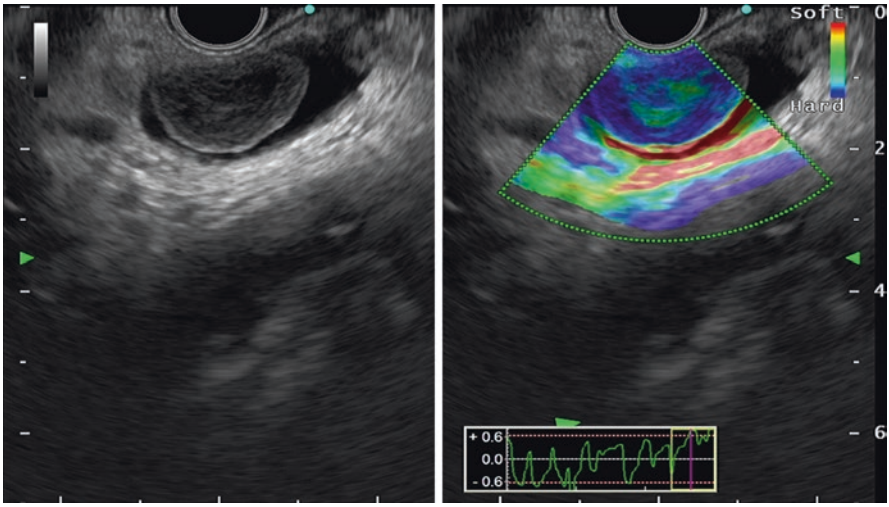

Fig. 3.10 EUS-E evaluation of a nodule within a pancreatic cyst. Fluids such as that contained in pancreatic cysts dampen the elastography strain rendering elastography often unreliable. In this case, a benign mucus plug appeared predominantly blue, which might have been misleading for the diagnosis of malignancy

especially in cases where a negative result of EUS-FNA is suspected or in patients unfit for EUS-FNA [36].

3.4 Conclusion

The introduction of CH-EUS and EUS-E to EUS routine has radically changed the diagnostic approach to pancreatic lesions. Differential diagnosis between benign and malignant lesions with high sensitivity but relatively low specificity is the main advantage of the techniques. Nevertheless, the final diagnosis remains histological through EUS-guided tissue acquisition.

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Endoscopic Ultrasound-Guided Tissue Acquisition of Solid Pancreatic Lesions

4

Laurent Monino and Pierre H. Deprez

Abbreviations

CEH	Contrast-enhanced harmonic
ESGE	European Society of Gastrointestinal Endoscopy
EUS	Endoscopy ultrasound
EUS-TA	Endoscopy ultrasound tissue acquisition
FNA	Fine-needle aspiration
FNB	Fine-needle biopsy
MOSE	Macroscopic on-site evaluation
ROSE	Rapid on-site cytopathologist evaluation

4.1 Introduction

Before the emergence of endoscopy ultrasound (EUS), the histological diagnosis of a solid pancreatic mass had to be made either by transcutaneous pancreatic puncture or by analysis of the surgical specimen. From the first EUS tissue acquisition (EUS-TA) with the reusable Vilmann fine-needle reported in 1992 [1], tissue acquisition from lesions within or adjacent to digestive tract guided with EUS has won its spurs in tumor diagnosis and patient management. First aiming at cytology sampling, needle tip evolution resulted in specimens with preserved histological architecture and improved diagnostic accuracy. In the literature, the diagnostic accuracy of EUS-TA for solid pancreatic masses varies between 78% and 95%, sensitivity 78% and 95%, and specificity 75% and 100% [2–8]. Moreover, with a

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low complication rate of around 1% [7, 9, 10], EUS-TA has become the technique of choice to characterize a solid pancreatic masse before surgical or medical management. In this chapter, we will describe the various techniques to perform EUS-TA and tips or tricks to improve diagnostic accuracy in most locations and situations.

4.2 The "Standard" Technique for EUS-TA

The first step of the EUS-TA is to identify the pancreatic lesion and to ensure the stability of the EUS scope as close as possible to the lesion. This is usually done by avoiding air insufflation, filling the tip balloon with water to anchor the scope in the duodenum, and to bend the scope tip with the up and down wheel fixed. It may be of interest to evaluate lesion mobility and hardness by applying pressure through the tip of the scope by increasing the upward pressure as much as possible in order to wedge the lesion against the probe. Then size, echogenicity (liquid or necrotic component), and vascularization have to be determined in the B and doppler modes. Highly vascular lesions should be punctured with caution, any vascular abnormality (pseudoaneurysm) should never be targeted. Puncture of necrotic area (avascular and hypoechoic) should be avoided since histological yield will be low. Once the lesion is well characterized, the surrounding area has to be examined carefully to detect any structure that should be avoided by the needle tract (vessels, CBD, pancreatic duct, excessive healthy pancreatic parenchyma).

In the second step, the needle is inserted into the operating channel, after removal of the operating channel cap, and the needle handle is attached to the end of the working channel (Fig. 4.1). If resistance is encountered in the scope, the needle should not be pushed excessively to avoid scope damage; check for excessive bending of the scope, especially with large-bore and stiff needles, and scope positioned in the duodenum. Bending of the scope should then be softened and wheels released. If the position is lost, the needle should be fully retracted in the scope to avoid luminal wall damage when maneuvering the scope. When resistance occurs at the tip of the needle, the scope elevator should be released to facilitate exit of the needle from the working channel. The lower locking knob control the length of the sheet protruding out of the scope. Usually set at 1–2 cm to allow the sheath tip to be just visible for 1–2 mm in the EUS field. Air should be suctioned to avoid bubble artifacts and excessive exit of the sheath (Fig. 4.2a–c). The presence of the needle (especially for 19G needles) in the working channel may have changed the position of the scope so that repositioning of scope tip and wheels may be necessary. The path of the needle is estimated and corrected by using the scope bending and elevator movements (so that the needle penetration angle is around 60°). The distance from the target to the needle tip is estimated, then the upper locking knob is unlocked and relocked at the desired distance (Fig. 4.3a–e). In most needles, the stylet has to be pulled 10 mm from the needle tip to facilitate penetration. Puncture can either be done in a fast movement till the locking knob position (preferred technique for hard lesions) or in a slow advancement to traverse the digestive wall

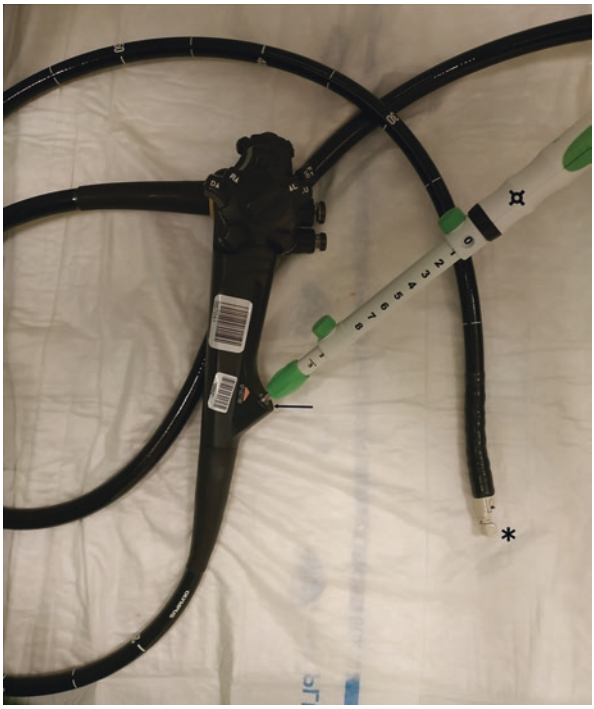

Fig. 4.1 Linear EUS scope with FNB inserted into the working channel (¤: FNB; *: linear EUS scope, Black arrow: working channel)

first, repositioning the needle if needed, and then pancreas and the lesion as deeply as possible under EUS control. At this stage, lateral movements should be avoided not to lose the EUS view of the needle tip that should be kept under control during the entire movement. It is indeed easier to follow the needle tip all along the tract, than to find it back at the end of puncture. In this case, if the tip is lost, we would suggest to do small movements torquing the scope laterally or using the small lateral scope wheel. If this is unsuccessful, needle should be slowly pulled back until the tip is again under full view and then advanced in the lesion.

The third step is the tissue acquisition itself; the stylet is removed from the needle, and a 10–20 mL syringe is attached to the needle to apply negative pressure. Several (usually ten are advised) to-and-from movements are performed within the lesion in a rapid forward and slower backward movement. The needle tip must remain visible during the to-and-fro movements. During the entire puncture phase, continuous aspiration of digestive lumen air and fluid must be maintained to improve vision. After a few passes through the lesion, suction should be stopped, and the needle is removed from the operating channel after placing the upper locking knob at the zero position, to avoid working channel damage. The punctured material is collected from the needle by injection of air or saline, or by insertion of the stylet and placed on slides and in the appropriate containers or tubes for cytohistological analysis. The specimen is evaluated macroscopically to check for the presence of sufficient material and, if possible, for a red or yellow core. More passes are done the same way either by flushing the needle with saline or air or by reinserting the stylet.

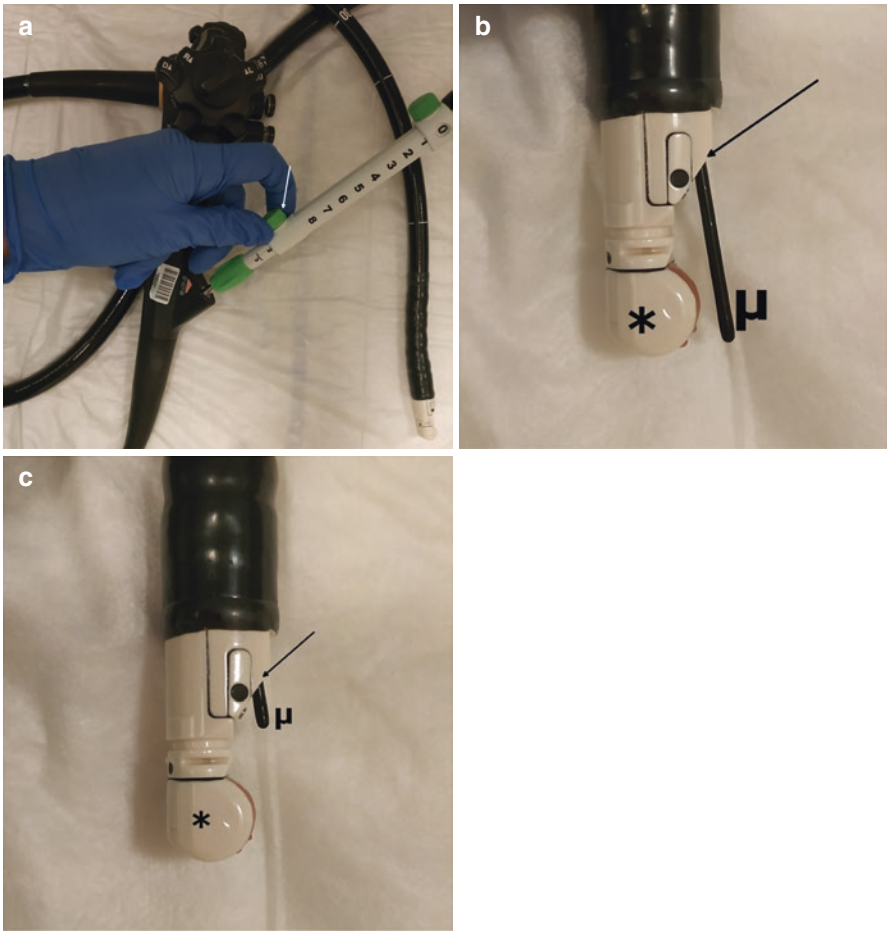

Fig. 4.2 The lower locking knob (white arrow); the needle sheath (μ); the end of the working channel (black arrow), tip of the linear EUS scope (*). (**a**) The lower knob is adjusted and locked at 1 or 2 cm, in this case at 2 cm. (**b**) View of the tip of the linear EUS scope, with an FNB needle inserted in the working channel. The end of the needle sheath is adjusted thanks to the lower knob, in this position at 3 cm mark, which is too long for safety. (**c**) It is preferable to avoid a too long extension of the needle sheath to facilitate bending of the needle, the sheath is therefore adjusted at 1 cm and locked at this position with the locking knob

In the majority of cases, solid malignant lesions of the pancreatic head develop in the upper two-thirds of the head and are therefore easily accessible by transduodenal access. Solid pancreatic lesions located in the body or tail are easily accessible by transgastric access. Solid pancreatic lesion of the uncus most often requires transduodenal D2 positioning making the puncture more difficult to succeed, due to a lower maneuverability of the scope and a lesion out of the needle tract. Solid pancreatic lesions of the neck are difficult to puncture because in transgastric access, the path of penetration is often tangential to the digestive wall,

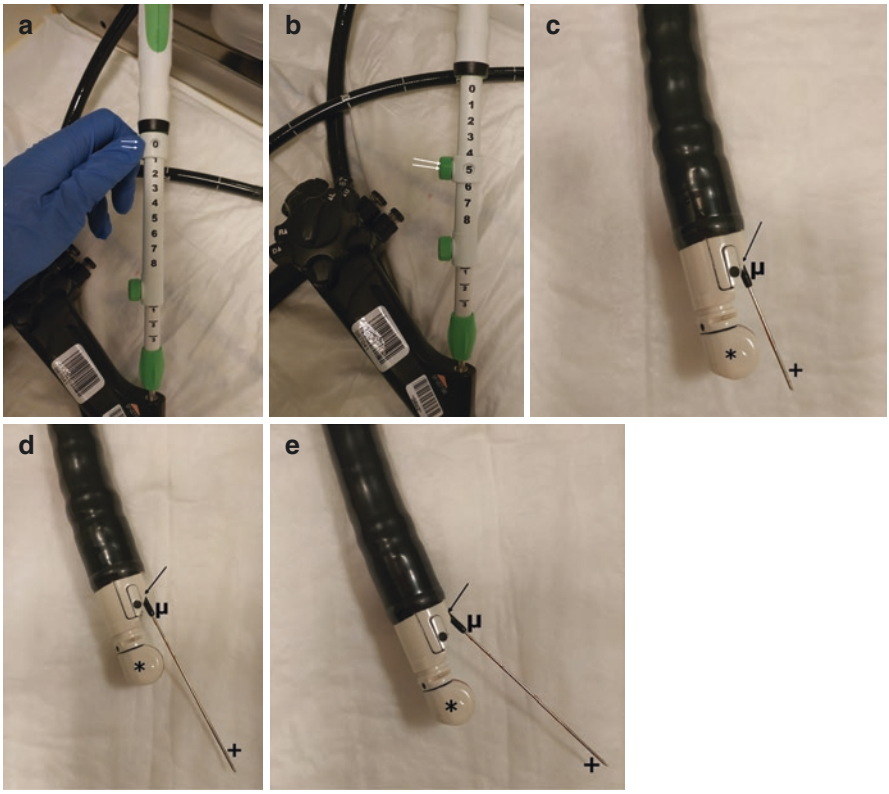

Fig. 4.3 The upper knob of the needle (two white arrows); the needle sheath (μ); the needle (+); the tip of the linear EUS scope (*). (**a**) The upper knob is unlocked and adjusted at the desired distance. (**b**) The upper knob is adjusted and locked at the 5 cm mark, meaning that the needle will extend to this length. (**c**) View of the tips of the linear EUS scope, needle sheath locked at the 1 cm mark, and needle tip locked at the 3 cm mark. (**d**) View of the tips of the linear EUS scope, needle sheath locked at the 1 cm mark, and needle tip locked at the 8 cm mark. (**e**) Same with elevator up. In this position, the elevator bends sheath and needle, but to accentuate needle bending, the sheath might be slightly retracted to apply the elevator force on the needle only

thus reducing the force of penetration and causing the digestive wall and lesion to be pushed back. An assistant or an endoscopic nurse may be required to help maintain a stable position of the EUS scope to increase the stability. Some echoendoscopists also use their knees to lock the EUS scope against the patient's bed, mimicking the flamingo posture. Most of the time, the puncture has to be done by a quick and dry gesture associated with blind phase feared by echoendoscopists. The "quick puncture" is carried out with a rapid and sharp movement, having previously fixed the blocker of the needle at the estimated distance to target the lesion center. If the lesion remains out of the needle tract, a smaller needle with higher bending ability should be used for better actuation. In some cases, a two-step puncture may be of help puncturing the wall first, then slightly advancing the scope

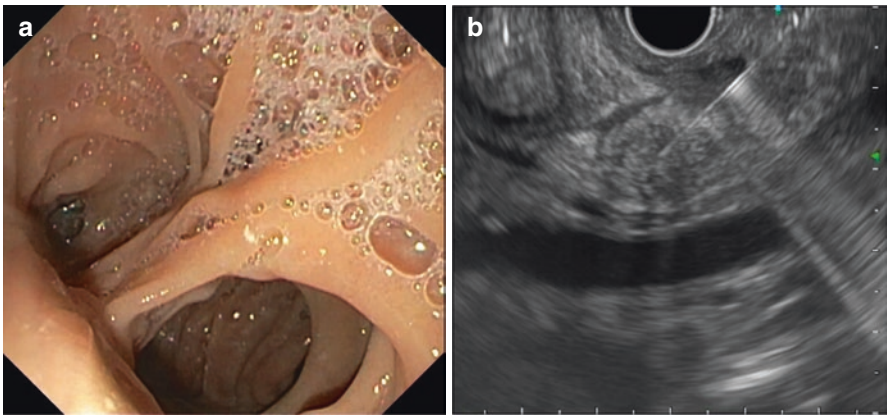

Fig. 4.4 Diagnosis of a solid pancreatic lesion in a patient with surgically altered anatomy. (**a**) Endoscopic view of the oesojejunal anastomosis, after total pancreatectomy. (**b**) FNB of solid pancreatic lesion of the body of the pancreas in a patient with surgically altered anatomy

to increase needle bending to a more perpendicular angle. For patients with surgically altered anatomy, it may still be possible to perform EUS-TA in the pancreas, but caution should be taken when advancing the scope in intestinal loops, more prone for perforation with the stiff EUS scopes [11] (Fig. 4.4a, b). In patients with Roux-en-Y gastric bypass, pancreas access may be obtained with a new minimally invasive and fully endoscopic approach using EUS-directed transgastric access (EDGE).

4.3 How to Improve the EUS-TA Performance in Solid Pancreatic Lesions?

4.3.1 The Fanning Technique

The fanning technique has been used by several expert endosonographers since the beginning of EUS-TA but was proved by Bang et al. [12] to improve the biopsy yield by limiting the number of passages. The fanning technique consists in modifying the needle penetration axis within the lesion by changing the up/down support of the EUS scope, by torquing the scope laterally, and by changing the elevator angulation. The needle path is changed between each up/down movement to cover a larger tumor area (Fig. 4.5a, b). In the study of Bang et al., the fanning techniques allowed a reduction in the number of passes and an improved diagnostic accuracy (96.4% with fanning technique vs. 76.9% without fanning). The proportion of patients in whom histological diagnosis was made after the first increased significantly compared with conventional technique passage (86% with fanning vs. 56% without fanning) [12]. The fanning technique therefore gained popularity and became the technique of choice for tissue acquisition of solid pancreatic lesion.

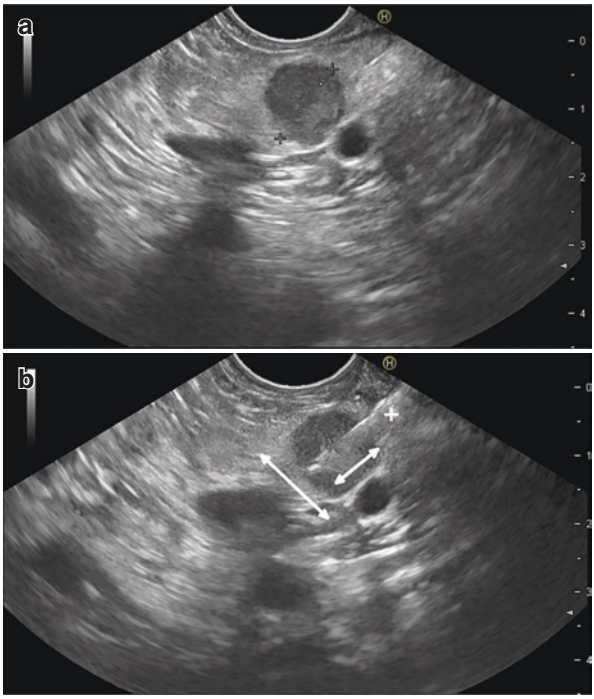

Fig. 4.5 EUS-TA of a solid lesion localized in the body of the pancreas: pancreatic metastasis of clear cell renal cell carcinoma (+: the needle; white arrows: corresponding of the to-and-fro movements of the needle combined with up/down movement of the elevator into the lesion). (**a**) Solid lesion of the body (size 17 mm): round, hypoechogenic, and homogenous. (**b**) Fine-needle biopsy with fanning technique; the path of the needle is changed at each movement with the use of the elevator, the up/down scope wheel, and scope torquing

Recently, Park et al. reported, in a prospective randomized controlled study, the use of the "torque technique" in solid pancreatic lesion [13]. It consists in twisting the EUS scope in a clockwise or counter clockwise position during the puncture. They found a significant difference in terms of the rate of preservation of histological architecture (standard vs. torque: 87.1% vs. 98.4% $p = 0.038$) and the quality of the histological sample (standard vs. torque: 79% vs. 93.5%, $p = 0.037$) compared to standard technique. Furthermore, diagnostic accuracy was higher with the torque technique than with the standard technique (96.8% vs. 87.1%). We therefore advise to perform fanning with all torquing, up-and-down, and elevator angulation movements.

4.3.2 Suction or Not

The use of suction during needle puncture has always been a subject of controversy [14, 15]. The use of suction during tissue acquisition increases the cell field and contamination of the sample with blood [16–18]. It appears that the use of a syringe with a volume of more than 10 mL does not improve histological performance and would increase the presence of blood contamination of the specimen [17, 19]. Practice with or without suction seems different from one continent to another. ESGE guidelines support the use of the negative pressure suction technique using 10 mL syringes with 22G or 25G needles [7]. We suggest to adapt the suction to the

type of lesion; a highly vascularized tumor (NET or renal cancer metastasis) should be punctured without suction to avoid excessive blood contamination, and harder less vascular lesions may benefit from suction to improve accuracy and sensitivity of histological diagnosis.

A combination of techniques, here again, may be of help; first pass without suction, and further passes with or without depending of the bloodiness of the first pass. Suction can also be applied through a needle filled with saline (wet suction technique). The effect of suction for the purpose of aspirating cells and/or tissue during fine-needle biopsy may be significantly improved by filling the column of the needle with a less compressible fluid. This effect would be most pronounced in larger gauge needles which would have a larger internal volume. A column of saline in the needle may increase the velocity of the pressure transfer providing more tissue and less blood. This method is supposed to transfer the negative pressure more efficiently from the syringe to the needle tip and to decrease damage to the cells and tissue, in absence or air vacuum. Wet suction cell blocks resulted in a significantly better diagnostic yield of 85.5% vs. 74.4% ($p < 0.0001$) [18].

4.3.3 FNB vs. FNA

There are two main EUS needle types on the market: FNA with acquisition of samples for cytological analysis and FNB with acquisition of specimens with preservation of tissue architecture for histological examination. This is not completely true, since FNA needles may provide histological specimens, depending on their sizes (histological yield from 19G > 22G > 25G).

Most FNA needles share the same tip design, but this is different for FNB needles. The first needles had a lateral hole [20] near the needle tip to improve tissue acquisition; the most widely used is the reverse bevel needle (Echotip ProCore 19G-22G-25G, Cook Medical, Inc., Winston-Salem, NC, USA) with the sharp edge of the lateral slit facing backwards to collect tissue during retrograde needle movement [21, 22]. The design was later modified due to some difficulties encountered when pulling back the needle in hard tumors into an antegrade core trap (Echotip ProCore 20G, Cook Medical, Inc., Winston-Salem, NC, USA) with the cutting edge facing forward to cut tissue during antegrade needle movement [23]. More recently, new needles were developed without a lateral hole, focusing the changes to their tips to increase their penetration and the tissue collection [24, 25]. Among them, the fork-sharped tip (SharkCore 19G-22G-25G, Medtronic, Minneapolis, MN, USA) with a fork-sharped needle tip with six cutting edges and an opposite bevel [26–28] and the Franseen tip geometry (Acquire 22G-25G, Boston Scientific Co., Marlborough, MA, USA) as a crown-shaped needle tip with three symmetrical, fully formed, cutting heels designed to maximize tissue capture and minimize fragmentation [29–31].

Several studies have been carried out comparing FNA and FNB but have not shown a significant difference in terms of diagnostic accuracy. The diagnostic

accuracy for FNA and FNB ranged from 84–92.5% to 90%, respectively [16, 32–35]. Most of these studies showed that quality of the histological sample was higher with the use of FNB than with FNA regardless of needle diameter [21, 30, 32, 34, 36]. A recent meta-analysis reported that there was no significant difference in diagnostic accuracy between the use of FNA and FNB. However, the number of needle passes was less important to achieve the histological diagnosis with an FNB [37]. In contrast to another recent meta-analysis which reported evidence that FNB ProCore outperformed FNA in the sampling of solid pancreatic or non-pancreatic lesion [38]. The debate between FNA and FNB is however slowly ending with the concept of individualized therapy in pancreatic cancer for which histologic large specimens are more appropriate for performing predictive molecular marker tests or cell cultures with chemosensitivity testing [39].

There are only few studies comparing the performance of EUS-guided fine-needle biopsy using fork-tip or side-fenestrated needles in patients with solid pancreatic lesions. A recent randomized controlled study compared sampling with fork-tip or side-fenestrated 22-gauge or 25-gauge needles. Three passes were performed, each independently evaluated by a blinded pathologist and by endosonographers for macroscopic on-site evaluation (MOSE). Both 22-gauge and 25-gauge fork-tip needles retrieved significantly higher rates of histologic samples than side-fenestrated needles ($P < 0.013$). Safety and diagnostic accuracy were comparable in the two arms, whereas sample quality (tissue integrity and blood contamination) was significantly better in the fork-tip group ($P < 0.0001$). The authors concluded that both needles showed equivalent safety and diagnostic accuracy. However, fork-tip needles provided a higher rate of extremely good-quality histologic samples and required fewer needle passes to reach a diagnosis [40].

4.3.4 Needle Diameter

Different needle sizes are commercially available for tissue puncture, ranging from 25 to 19G. With a large diameter (19G or 20G), the amount of tissue and core punctured is more important allowing for an increased diagnostic accuracy. Achieving bigger tissue acquisitions seems now the main target, and this is reflected by the ESGE guidelines suggesting to use 19G FNA or fine-needle biopsy (FNB) needles or 22G FNB needles when the primary aim of sampling is to obtain core tissue (low-quality evidence, weak recommendation) [7]. These indications include well-differentiated adenocarcinomas, autoimmune pancreatitis, and sarcoidosis. Moreover, providing histological samples that yield an adequate amount of tumor cells and desmoplastic stroma suitable for molecular analysis. However, these large-bore needles have never been popular among endosonographers, mainly due to their stiffness and known technical failures, especially when used transduodenally. A multicenter randomized prospective study compared standard 22G needles with 19G nitinol needles for transduodenal EUS-guided FNB. Despite improved flexibility, the 19G nitinol needle was still associated with a higher failure rate and

lower diagnostic accuracy, although the quality of the specimen obtained was not different between the needles. This signed the unplanned but proven obsolescence of large-bore EUS needles in the pancreas [41].

Smaller diameter needles on the opposite are more flexible, therefore increasing their maneuverability, reducing blood contamination of the sample, and allowing targeting of hard-to-reach areas [42]. The choice of needle diameter should therefore depend on the target lesion; for small lesions (<10 mm), and/or hypervascular, and/or difficult to access (transduodenal or through a large vessel or when the puncture path traverses a large area of healthy pancreatic parenchyma), it would be preferable to choose a small diameter needle (25G). The disadvantage of thin needles is the small sample size, most of the time only allowing for cytological smears. Most of the comparisons between different needles diameters showed no significant differences. Concerning FNA needles, among other studies, Song et al. [43] reported that there was no significant difference in diagnostic accuracy between 19G and 22G needles (87% vs. 79%), but a better diagnostic accuracy in case of technical success for malignant lesions using 19G needles (95% vs. 79% $p = 0.015$). The number of passages for the 19G needle was statistically lower compared to the 22G needle. However, the technical success rate was higher for pancreatic head lesions with 22G needles than with 19G needles (100% vs. 81% $p = 0.019$).

Concerning FNB needles, the comparison between 25G and 22G did not reveal any significant difference in terms of sample quality or diagnostic accuracy [44]. However, Park et al. recommended the use of a 25G needle in difficult positioning situations due to technical difficulties. Two recent meta-analysis have shown that the use of 25G FNA probably has better diagnostic performance than 22G needles [45, 46]. Their results showed better sensitivity with 25G needles than with 22G needles (0.90 vs. 0.87, chi-deux 5.26, $p = 0.02$, 45). Several studies have compared large-diameter FNA needles with smaller-caliber FNB [47, 48]. These studies did not show significant differences in terms of diagnostic accuracy. In a recent meta-analysis, no significant difference was found in terms of diagnostic accuracy, sample size, and histological sampling rate in the case of solid pancreatic lesions [49]. Identical results were found in another meta-analysis for the diagnostic accuracy of malignant lesion [50]. Moreover, they did not show significant differences in terms of adverse events (RR:1.26; 95% IC 0.34–4.62) and technical failure (RR:5.07; 95% IC 0.68–37.64).

But again diagnostic accuracy is not the sole or even main issue; the amount of material is now the issue in expert cancer centers to provide sufficient material for ancillary techniques and individualized therapy, and this is better achieved with 22G FNB needle. REF.

4.3.5 ROSE or MOSE?

The presence of a cytopathologist in the endoscopy room during EUS-TA (ROSE) has been shown initially to improve diagnostic accuracy with cytological smears. The presence of a rapid on-site cytopathologist was more widespread in American

teams (98%) than in European (48%) or Asian teams (55%) [51]. A meta-analysis on the presence of ROSE reported an improvement of the diagnostic sensitivity of EUS-FNA for pancreatic solid masses from 88% to 95% compared with 80% in the absence of cytopathologist [52]. On the contrary, a meta-analysis of Kong et al. did not report an increase in diagnostic sensitivity with the use of ROSE [53]. Recently, with the introduction of FNB, another meta-analysis concluded on the absence of significant difference in diagnostic accuracy between FNA with ROSE and FNB alone [54]. Moreover, cost effectiveness studies showed a significant cost increase when using ROSE, explaining the lower popularity of ROSE in Europe where cytopathology is less reimbursed and histology preferred for diagnosis in pancreatic tumors [55, 56].

The use of macroscopic on-site evaluation (MOSE) to estimate the adequacy of a specimen for histological diagnosis during endoscopic ultrasound (EUS)-guided fine-needle tissue acquisition (FNTA) has also been advocated. A recent international, multicenter, prospective, randomized controlled study compared consecutive adult patients referred for EUS-FNTA for solid lesions larger than 2 cm who were randomized to a MOSE arm or to a conventional arm without ROSE. The diagnostic yield for the MOSE technique (92.6%) was similar to that for the conventional technique (89.3%; $P = 0.37$), with significantly fewer passes made (median: conventional 3, MOSE 2; $P < 0.001$). This implies that MOSE is an interesting evaluation when performing FNB with fewer passes and without the extra cost of ROSE [57].

4.3.6 Ancillary Techniques

Contrast-enhanced harmonic (CEH) has been proposed as an ancillary technique to guide the endoscopist to select a "profitable" area (avoiding fibrotic or necrotic areas) in solid pancreatic lesion and to increase diagnostic accuracy and sensitivity [58, 59]. The use of CEH in solid pancreatic masses may reduce the number of needle passes required to obtain a histological diagnosis Sugimoto et al. showed that CEH-EUS significantly reduced the number of needle passes required to obtain sufficient biopsy samples [60]. In a retrospective study, the diagnostic accuracy of EUS-FNA was improved with CEH (96.6% vs. 86.7%, respectively) but without statistical difference ($p = 0.054$) [51]. Another study of Seican et al. reported the same superiority of CEH-EUS/FNA (86.5% vs. 78.4% for EUS FNA) without statistical significance ($p = 0.35$) [58]. To date, no study has been able to demonstrate a significant superiority in diagnostic accuracy with the use of CEH. The same is true for elastography that determines the lesion hardness by means of a color code or semiquantitative measures, and thus the neoplastic or inflammatory nature of a lesion (Fig. 4.6). Some studies have tried to show an increased diagnostic accuracy by using elastography to guide the best location for fine-needle puncture [52, 53], without significant difference. Whether the two techniques combined, elastography and CEH-EUS, might significantly improve diagnostic accuracy during FNA and even more FNB still need further evaluation [54]. These techniques are for sure not

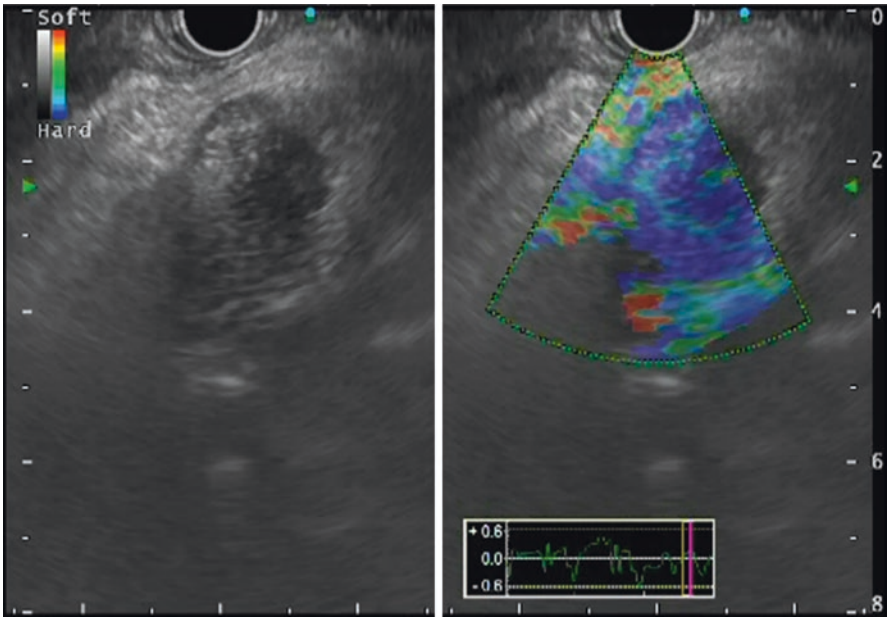

Fig. 4.6 Endoscopic ultrasound elastography of a pancreatic solid lesion of the body; adenocarcinoma of the pancreas (blue corresponding of hard part of the lesion)

first-line tools, but might be of help in FNA or FNB failures to better target the optimal site for puncture.

4.3.7 Reducing Adverse Events

The rate of adverse events reported during EUS-TA ranges from 1% to 8% [7, 9, 10], and in the pancreas for solid pancreatic masses around 1% [55, 56, 61]. The main adverse events are acute pancreatitis, bleeding, infectious complications (including biliary peritonitis), and needle tract seeding. Most adverse events appear in the first 7 days after the tissue acquisition [56, 61] and are more frequent in small size lesions (<20 mm) and neuroendocrine tumors [62]. Needle diameter does not seem to be associated to a higher risk for complication [55]. A meta-analysis compared the adverse events rate between FNB and FNA and strangely showed a lower risk with FNB than with FNA (0.59% vs. 0.98%) [61].

EUS FNA and EUS-FNB are considered by all scientific societies (ESGE, ASGE and APAGE/APSDE) as high-risk procedures for hemorrhage, especially in the pancreas, although the risk for bleeding during EUS-TA is reported less than 0.13% [10, 63–65]. Some reports have even not shown any increased significant risk for bleeding in patients taking aspirin, antiplatelets, or antithrombotic agents [63].

These societies recommend to continue aspirin and to stop clopidogrel/prasugrel or ticagrelor 5 days before performing EUS-guided tissue acquisition for patients

with a low-risk condition of cardiovascular events. In case of patients with a high-risk condition of cardiovascular events (recent insertion of a coronary stent), it is generally recommended to discuss with the cardiologist for considering stopping antiplatelet treatment or postponing the EUS-TA. For direct oral anticoagulants (DOAC), they recommend to take the last dose >48 h before EUS-TA, and specifically for dabigatran associated with renal insufficiency, to take the last dose >72 h before EUS-TA. For vitamin K antagonist, they recommend to stop them 5 days before performing EUS-TA and to consider bridging with LMWH in patients with a high risk of thrombosis. For LMWH users, the last dose of LMWH should be given >24 h before procedure and restarted in the evening of the procedure.

Infectious complications after EUS-TA of solid pancreatic masses are very rare with post-puncture fever rate reported at 0.08% and infection rate at 0.02%, in the meta-analysis of Wang et al. [10]. The use of antibiotics before, during, or after the puncture as a routine procedure is not recommended for solid pancreatic lesions [7].

The risk of acute pancreatitis after puncture is low, around 1–2% [7, 9, 61]. Risk factors have been highlighted such as the small lesion size, neuroendocrine tumors, a recent history of acute pancreatitis, more than 5 mm of healthy parenchyma traversed by the needle, and puncture of the main pancreatic duct [62, 66]. The type of needle does not appear to increase the risk of acute pancreatitis, with rates of acute pancreatitis of 0.44% and 0.19%, during EUS-FNA and FNB, respectively [55]. Biliary peritonitis is a rare complication encountered only in lesions of the head of the pancreas when the needle path passes through the common bile duct [9].

The risk of needle tract seeding is extremely rare. There are some reported cases of seeding in the gastric wall or in the peritoneal cavity [67, 68]. According to the study by Ngamruengphong et al., preoperative EUS-FNA was however not associated with an increased rate of cancer recurrence in the stomach wall or peritoneum [69]. On the contrary to advanced unresectable cancers, the risk for seeding should be better assessed for resectable or borderline lesions, since it may worsen prognosis. In such cases, a needle type that increases histological efficiency (or diagnostic accuracy) with a single pass through the lesion should be preferred, and a transduodenal puncture tract chosen to avoid peritoneal seeding, if feasible.

4.4 Conclusion

With its low rate of adverse events and high diagnostic accuracy, EUS-TA has become a safe and irreplaceable technique in the management of solid pancreatic lesions. In this chapter, we detailed the techniques to perform a puncture in almost any situation, with the most appropriate needle and technique. Several tips and tricks were shown to ensure a high diagnostic accuracy. Most studies demonstrate indeed that a 90–95% diagnostic accuracy can be achieved with the new FNB needles, with only a few passes if MOSE is part of the puncture. This high efficiency combined with the sampling of larger histological specimens offers the opportunity to consider precision therapy based on molecular and genomic profiling of tumors, and even cell cultures with chemosensitivity testing.

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5 Evidence-Based Assessment of Diagnostic Performance of Currently Available Needles and Techniques for EUS-Guided Tissue Acquisition

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Key Points

- Several technical and clinical features are known to influence the diagnostic performance of EUS-FNA, including location, size and tissue firmness of the lesion, experience of the endoscopist, and availability of rapid on-site evaluation (ROSE) of EUS-FNA samples performed by a cytopathologist.
- The development of EUS fine-needle biopsy (EUS-FNB) needles has generated a great deal of interest in the field of EUS-tissue acquisition (TA) primarily based on proposed advantages over EUS-FNA of improving diagnostic accuracy, improving procurement of samples with preserved tissue architecture, and allowing for immunohistochemistry obviating ROSE and obtaining results in fewer passes.
- In over past 2–3 years, there have been significant paradigm changes in tip of EUS-FNB needle designs, with newer FNB needles introduced in the endoscopic practice; although these novel needle designs are thought to improve tissue capture and several studies have been published testing these novel devices, there is still limited evidence on their diagnostic performance in terms of diagnostic yield and histology core procurement.
- Through-the-needle biopsy and needle-based confocal laser endomicroscopy represent invaluable newer tools for the diagnosis and characterization of pancreatic cysts.

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5.1 Introduction

Endoscopic ultrasound (EUS) represents a valuable and accurate diagnostic technique for the morphological characterization of pancreatic lesions; furthermore, EUS allows sampling of pancreatic tissue for cytopathological diagnosis by means of fine-needle aspiration (FNA) [1, 2].

However, several technical and clinical features are known to influence the diagnostic performance of EUS-FNA, including location, size and tissue firmness of the lesion [3], experience of the endoscopist [4], and availability of rapid on-site evaluation (ROSE) of EUS-FNA samples performed by a cytopathologist [5]. On the other hand, whether specific procedural aspects such as use of a stylet, number of needle passes, or different needle sizes may have an impact on diagnostic accuracy and sample adequacy is still a matter of debate [6–9].

In spite of the good results observed with EUS fine-needle aspiration (EUS-FNA) and the recent developments in this field, such as use of rapid on-site evaluation (ROSE) [10], contrast-enhanced–guided FNA [11, 12], or tissue elastography [13], diagnostic sensitivity still remains an issue. Thus, the most important pitfall associated with this procedure is a false-negative diagnosis that has the potential to delay patient care and negatively impact patient outcomes.

The development of EUS fine-needle biopsy (EUS-FNB) needles has generated a great deal of interest in the field of EUS-tissue acquisition (TA) primarily based on proposed advantages over EUS-FNA of improving diagnostic accuracy, improving procurement of samples with preserved tissue architecture, and allowing for immunohistochemistry or special stains required for certain diagnoses, obviating ROSE and obtaining results in fewer passes and thus potentially improving the efficiency and costs associated with EUS-TA [14].

In over past 2–3 years, there have been significant paradigm changes in tip of EUS-FNB needle designs, with newer FNB needles introduced in the endoscopic practice; however, although these novel needle designs are thought to improve tissue capture and several studies have been published testing these novel devices, there is still limited evidence on their diagnostic performance in terms of diagnostic yield and histology core procurement.

The aim of this chapter is to provide an updated evidence-based state-of-art in the field of EUS-TA based on recent series and meta-analyses published on this topic.

5.2 EUS-FNA

5.2.1 Needle Size

EUS-FNA is a useful technique for diagnosis and staging of lesions in and around the proximity of gastrointestinal tract. For diagnosis of solid pancreatic lesions, sensitivity and specificity of EUS–FNA are 85–89% and 96–99% [15, 16], whereas for pancreatic cystic lesions are 54% and 93%, respectively [17].

Optimal tissue acquisition from lesions depends on various factors such as needle sizes and gauges, presence of cytotechnologists for rapid on-site evaluation (ROSE), expertise of endoscopist, and tissue handling techniques [1].

Among the needles more frequently used in EUS-FNA, 22G and 25G have gained increasing popularity due to their manageability and safety [9]. Theoretically, larger needles (for instance, 22G or even 19G) allow the collection of larger samples but may lead to an increased rate of complications. Moreover, they may cause some technical problems mostly due to higher stiffness of the device, likelihood of bloody contamination, or presence of cellular debris in the sample.

Due to these potential drawbacks of larger needles, 25G needle has been successfully introduced in the clinical practice.

A previous meta-analysis published in 2013 found a significant superior sensitivity of 25G over 22G (93% vs. 85%; $p = 0.0003$) while specificity was similar (100% and 97% with 22G and 25G, respectively, $p = 0.97$) [9].

A more recent meta-analysis of only randomized-controlled trials (RCTs) published by our group found that there is no significance difference in terms of sensitivity between the two FNA needles [18]. In fact, as reported in Fig. 5.1, pooled sensitivity of 22G needle was 89% (95% CI: 85–94%) while sensitivity of 25G

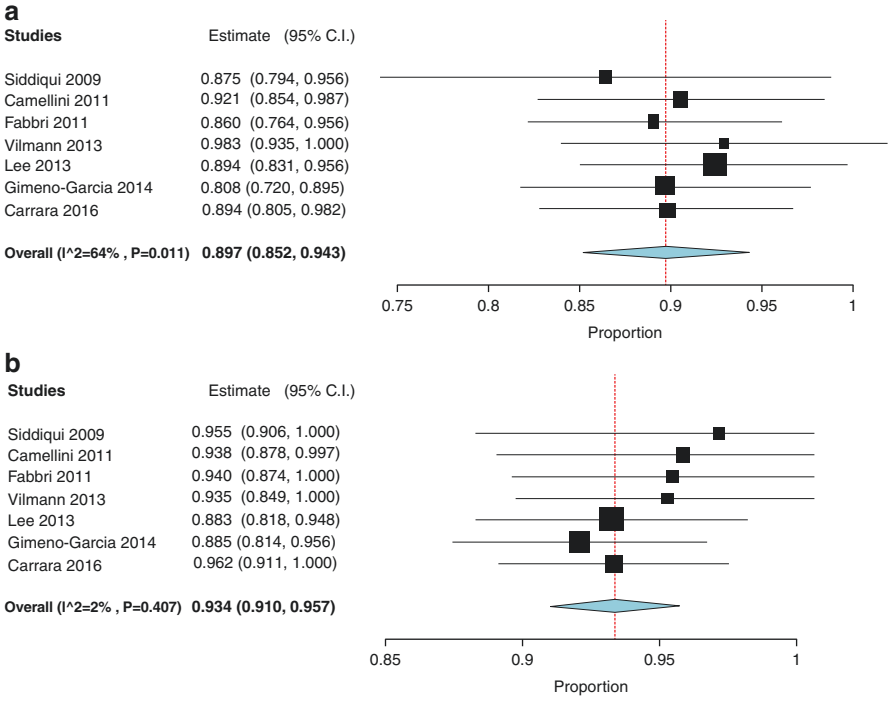

Fig. 5.1 Pooled sensitivity of (**a**) 22G and (**b**) 25G fine-needle aspiration for sampling solid pancreatic masses. Pooled sensitivity of 22G needles was 0.89 (95% CI: 0.85–0.94) while sensitivity of 25G needles was 0.93 (0.91–0.95)

Table 5.1 Main systematic reviews comparing 22G and 25G fine-needle aspiration for sampling solid pancreatic masses

Study	Included studies	Main outcomes
Xu, 2017 [24]	7 RCTs and 4 prospective studies	Higher pooled sensitivity for malignancy for the 25G needle vs. 22G needle (92% vs. 88%, p = 0.046) Similar area under the summary ROC curve (0.96 for the 25G needle and 0.97 for the 25G needle)
Facciorusso, 2017 [18]	7 RCTs	Pooled sensitivity: 25G needle, 93% vs. 22G needle, 89%; $p = 0.13$ The area under the ROC curve was 0.99 for the 25G needle and 0.98 for the 22G needle
Madhoun, 2013 [9]	3 RCTs, 2 prospective and 3 retrospective studies	Higher sensitivity for the 25G needle vs. 22G needle (93% vs. 85%; $p < 0.001$) The difference in sensitivity was nonsignificant when only prospective studies were analyzed (94% vs. 87%)
Affolter, 2013 [25]	5 RCTs, 3 prospective and 3 retrospective studies	Similar accuracy: $p = 0.97$ Pooled sensitivity: 25G needle, 91% vs. 22G needle, 78%

RCTs randomized-controlled trials

needle was 93% (91–95%) ($p = 0.13$). Likewise, also sample adequacy resulted similar between the two needles (risk ratio: 1.03, 0.99–1.07; $p = 0.12$); therefore, the potential advantages of larger needles (ability to collect larger tissue samples) seem to be balanced by the easier use of 25G needle through the pancreatic tissue [18].

Both the EUS-FNA needles proved to be absolutely safe with no severe adverse events registered [9, 18].

19G needles are used primarily to obtain samples with preserved tissue architecture adequate for histologic evaluation [19]. These needles are stiffer and more difficult to operate as compared to thinner needles, especially when sampling is performed with the scope in an angulated position, for example, from the duodenum [20–22]. A 19G FNA needle made out of nitinol was shown to offer mechanical performance advantages in benchtop testing [21] but a recent French RCT found this device significantly inferior to standard 22G needle [23].

Based on these evidences, current European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend for routine EUS-guided sampling of solid masses both 25G or 22G needles (high-quality evidence, strong recommendation) [19].

Table 5.1 reports the main systematic reviews [9, 18, 24, 25] published in the field.

5.2.2 Suction

Results of two RCTs indicate that using 10 mL of suction during sampling with 22G or 25G FNA needles improves accuracy and/or sensitivity for malignancy when

compared to the no suction technique [26, 27]. The evidence in favor of suction is strongest for 22G FNA needles in the setting of pancreatic masses and it is less clear for sampling with 25G FNA needles. Although the evidence on the effect of using suction is somehow limited, there are also no perceivable risks or disadvantages of this technique. Increased sample bloodiness shown in some studies does not appear to affect diagnostic performance and as a result does not constitute a significant problem. Therefore, the aforementioned ESGE guidelines decided to recommend using suction for all indications and all needle gauges and types in EUS-TA [19].

While slow removal of the stylet during sampling aiming to enhance sample adequacy by creating minimal negative pressure within the needle ("stylet slow-pull" technique) provided discording results [28, 29], eliminating the residual negative pressure by disconnecting the syringe stopcock from the needle port before withdrawing the needle from the target lesion was shown to increase diagnostic outcomes [30]. Therefore, although the mechanism behind this effect remains uncertain and the evidence is limited, this simple maneuver is recommended by current guidelines [19].

Seven RCTs so far compared slow-pull technique with standard suction for sampling solid pancreatic lesions [28–34], and main results of the published evidence are reported in Table 5.2. A recent meta-analysis concluded for a non-superiority of

Table 5.2 Randomized-controlled trials comparing slow-pull to suction technique for sampling solid pancreatic masses

Study	Country	Needle	Number of patients	ROSE	Diagnostic accuracy
Saxena, 2017 [28]	USA	22G (Expect Slimline®; Boston Scientific), FNA	121	Yes	Slow-pull: 80% (68.1–88.2%) Suction: 70% (57.3–80.2%)
Bansal, 2017 [29]	India	22G (EchoTip Ultra HD®; Cook), FNA	36	No	Not reported
Weston, 2017 [30]	USA	22G and 25G (ProCore®; Cook Medical), FNB	60	No	Not reported
Lee, 2018 [31]	Korea	22G (Expect Slimline®; Boston Scientific), FNA	48	No	Slow-pull: 88% (75.4–94.6%) Suction: 71% (56.8–82%)
Cheng, 2019 [32]	Brazil	22G (Expect Slimline®; Boston Scientific; Sonotip®, Medi-Globe GmbH), FNA	50	No	Slow-pull: 82% (68.9–90.4%) Suction: 90% (78.1–95.8%)
Di Mitri, 2019 [33]	Italy	20G (ProCore®; Cook Medical), FNB	48	No	Slow-pull: 85% (71.6–92.7%) Suction: 85% (63.1–94.9%)
Lee, 2019 [34]	Korea	22G and 25G (ProCore®; Cook Medical), FNB	50	No	Not reported

FNA fine-needle aspiration, *FNB* fine-needle biopsy

slow-pull over standard suction (odds ratio for adequacy = 0.98), although slow-pull resulted in reduced blood contamination (pooled rate 10.5% vs. 17.8%) [35].

5.2.3 Stylet

The main aim of using stylet is to prevent blockade lumen of needle as it passes though the gastrointestinal wall. Studies have reported similar diagnostic yield and specimen adequacy with and without stylet [36–39]. The potential above cited advantages of using the stylet have not been proven, and there is high-quality evidence that sampling using 22G FNA needles with or without the stylet provides samples of similar quality and adequacy. On the other hand, potential disadvantages, such as the risk of needlestick injury during stylet manipulation, increased procedure time, and decreased needle flexibility have not been evaluated and their significance remains uncertain. In this situation, current guidelines decided not to recommend for or against using the stylet for sampling with FNA needles, leaving this to the discretion of the endosonographer [19].

5.2.4 ROSE

The main objectives of ROSE are to provide real-time feedback during endoscopy regarding the content and adequacy of specimen, to minimize the number of passes, to decrease inadequate samples, and to increase efficiency of procedure. In spite of these theoretical advantages, available studies provide discording results with the fewer number of passes being the only unequivocal advantage of ROSE shown in all the published literature [10, 40].

ROSE is unavailable in about half of the EUS centers in Europe. Furthermore, ROSE is unavailable in most centers outside of the USA; therefore, ESGE guidelines did not find sufficient reasons to recommend that centers not using ROSE should change their practice [19].

5.2.5 Fanning Technique

The fanning technique involves positioning the needle at four different areas within the mass and performing four back-and-forth movements in each of them to procure tissue while the standard targeting technique involves positioning the needle at one location within the mass and performing 16 back-and-forth movements to procure tissue. In an RCT in patients with pancreatic masses, use of a fanning technique, compared to the standard targeting technique, decreased the number of needle passes required to establish the diagnosis and increased the proportion of patients in whom an on-site diagnosis was achieved on the first pass [41]. Based on this single RCT, ESGE suggests fanning the needle throughout the lesion when sampling solid masses (moderate-quality evidence, weak recommendation) [19].

5.3 EUS-FNB

5.3.1 General Concepts

In order to overcome at least partially the aforementioned limitations of FNA and given the pressing need of adequate histological samples for molecular analysis, biopsy needles have been developed and introduced in the clinical practice.

The first flexible biopsy needle (Quick-Core®) was introduced in early 2000s and adapted from the TruCut design but its performances were impaired by several technical issues such as challenges in deploying the spring-loaded tray when in torqued positions within the duodenum, as well as loss of specimen when the needle was withdrawn [42]. As a consequence, TruCut needle failed to determine a significant increase in diagnostic outcomes as compared to standard FNA needles, thus limiting its use worldwide.

Although ProCore® biopsy needle seems to address most of the limitations of previous biopsy devices, thanks to the addition of a reverse bevel just distal to the tip promoting collection of a core sample, no significant differences in adequate tissue acquisition, diagnostic accuracy, and rate of histological core specimen acquisition were seen with a significantly lower number of passes being the only advantage observed with FNB as compared to standard FNA [43–45].

The two most recently introduced EUS-FNB needles are end-type cutting needles of markedly different design. One is a Franseen needle (Acquire®, Boston Scientific, Marlborough, MA), which is a three-plane symmetric needle. The other (SharkCore®, Medtronic Inc., Sunnyvale, CA) is described as a fork-tip needle, though there are actually six cutting surfaces in an asymmetric design [42].

5.3.2 Comparative Effectiveness of Different FNB Needles

Published trials comparing FNB to standard FNA [46–58] are reported in Table 5.3.

A recent pairwise meta-analysis comparing 22G FNB vs. 22G FNA showed that the two needles resulted comparable in terms of either diagnostic accuracy (risk ratio [RR] 1.02, $p = 0.46$) or sample adequacy (RR 1.01, $p = 0.61$) [44]. Likewise, histologic core procurement rate (RR 1.01, $p = 0.86$) and pooled sensitivity were similar with both devices (93.1% with FNB and 90.4% with FNA) [44]. Of note, FNA led to competitive results in comparison to FNB even in absence of ROSE (as usual in non-American series) [44]. Most of the included trials used ProCore® needles, while Franseen biopsy needle (Acquire®) showed significant benefit concerning high-quality histologic yield (RR 1.18, $p = 0.02$) although this finding was based on a single American study [48], thus limiting the quality of evidence [44].

A recent network meta-analysis published by our group observed that there was no significant difference in diagnostic accuracy between different EUS-TA approaches for sampling pancreatic masses, based on low-quality evidence [59]. This striking result, which is in contrast to current evidence on other lesions such as subepithelial masses [60], was confirmed for all of the outcomes evaluated,

Table 5.3 Randomized-controlled trials comparing endoscopic ultrasound-guided fine-needle biopsy and fine-needle aspiration for sampling solid pancreatic masses

Study	Arms	Number of patients	Country	Lesion size (cm)	ROSE	Needle	Main outcomes
Alatawi, 2015 [46]	22G FNB 22G FNA	50 50	France	3.2 ± 0.5 3.3 ± 0.2	No	ProCore® Echo Ultra®	FNB: 98% accuracy 100% adequacy FNA: 90% accuracy 90% adequacy
Bang, 2012 [47]	22G FNB 22G FNA	28 28	USA	3.2 ± 0.9 3.3 ± 0.7	Yes	ProCore® Expect®	FNB: 89.2% accuracy 89.2% adequacy FNA: 100% accuracy 100% adequacy
Bang, 2017 [48]	22G FNB 22G FNA	46 46	USA	2.9 ± 0.8	Yes	Acquire® Expect®	FNB: 93.5% accuracy 100% adequacy FNA: 80.4% accuracy 95.6% adequacy
Cheng, 2017 [49][a]	22G FNB 22G FNA	123 126	China	2.91 2.95	No	ProCore® EchoTip®	FNB: 89.4% adequacy FNA: 84.9% adequacy
Ganc, 2014 [50][b]	22G FNB 22G FNA	30 30	Brazil	NR	No	ProCore® EchoTip®	FNB: 93.3% accuracy FNA: 90% accuracy
Hucl, 2013 [51][a]	22G FNB 22G FNA	69 69	India	4.19 ± 1.7	No	ProCore® EchoTip®	FNB: 85.5% accuracy 92.7% adequacy FNA: 73.9% accuracy 86.9% adequacy
Lee, 2017 [52][b]	22G FNB 22G FNA	9 7	Korea	4.4 ± 3.2 3.7 ± 2	No	ProCore® EchoTip®	FNB: 100% adequacy FNA: 100% adequacy
Noh, 2017 [53]	22G FNB 22G FNA	60 60	Korea	3.1 ± 0.8	No	ProCore® EZShot 2®	Not reported
Othman, 2017 [54][c]	22G FNB 22G FNA	29 60	USA	NR	Yes	ProCore® EZShot 2®/ Expect®	FNB: 72.4% adequacy FNA: 68.3% adequacy

Sterlacci, 2016 [55][a]	22G FNB 22G FNA	38 38	Germany	3.3 ± 1.2	No	ProCore® EchoTip®	FNB: 89.5% adequacy FNA: 97.3% adequacy
Vanbiervliet, 2014 [56]	22G FNB 22G FNA	80 80	France	3.3 ± 1	No	ProCore® EchoTip®	FNB: 88.7% adequacy FNA: 93.7% adequacy
Mavrogenis, 2015 [57][a]	25G FNB 22G FNA	19 19	Belgium	3.9 (1–7)	No	ProCore® EchoTip®	FNB: 73.6% accuracy 84.2% adequacy FNA: 68.4% accuracy 78.9% adequacy
Kamata, 2016 [58]	25G FNB 25G FNA	106 108	Japan	2.93 ± 1.5 2.79 ± 1.4	No	ProCore® EchoTip®	FNB: 79.2% accuracy 100% adequacy FNA: 75.9% accuracy 100% adequacy

FNA fine-needle aspiration, *FNB* fine-needle biopsy, *NR* not reported, *ROSE* rapid on-site evaluation

[a]Trials including both pancreatic and extra-pancreatic masses. Only pancreatic lesions were reported in the table and included in the analysis

[b]Conference abstract

[c]Three-arm trial comparing two different FNA needles and FNB. Data from the two FNA arms were merged

including sample adequacy and histological core procurement. Therefore, needle design (whether FNA or FNA) and gauge (19G, 22G, or 25G) did not seem to impact significantly the diagnostic performance of the procedure [59].

The main findings of the above cited network meta-analysis [59] are reported in Table 5.4. The overall body of evidence was rated down for serious risk of bias, since the included RCTs were unblinded and at high risk of performance bias. Furthermore, for several comparisons, evidence was rated down due to imprecision [59].

These results suggest that EUS-FNA would suffice for most cases in routine clinical practice (patients with pancreatic adenocarcinoma) and add credence to the recently published European guidelines that equally recommend FNA and FNB for routine sampling of solid masses [19]. FNB is likely to play a pivotal role for conditions that require assessment of tissue architecture, and it would be the preferred modality in these situations (for example, in oncologic studies that require core biopsies for personalized medicine or benign conditions such as autoimmune pancreatitis) [61].

Table 5.4 GRADE assessment of quality of evidence informing the comparisons between different needles for endoscopic ultrasound-guided tissue sampling of solid pancreatic masses

Needle	Diagnostic accuracy		Sample adequacy	
	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence
All needles vs. 19G FNA				
22G FNA	1.06 (0.80, 1.41)	Low	1.14 (0.87–1.51)	Low
22G FNB	1.10 (0.80, 1.50)	Low	1.17 (0.89–1.53)	Low
25G FNA	1.10 (0.81, 1.51)	Low	1.19 (0.83–1.55)	Low
25G FNB	1.16 (0.58, 1.69)	Low	1.20 (0.89–1.61)	
vs. 22G FNA				
22G FNB	1.03 (0.89, 1.18)	Low	1.02 (0.94–1.16)	Low
25G FNA	1.03 (0.91, 1.17)	Low	1.04 (0.93–1.21)	Low
25G FNB	1.09 (0.85, 1.39)	Low	1.05 (0.92–1.19)	Low
vs. 22G FNB				
25G FNA	1.00 (0.83, 1.20)	Low	1.02 (0.93–1.17)	Low
25G FNB	1.05 (0.82, 1.36)	Low	1.03 (0.94–1.11)	Low
vs. 25G FNA				
25G FNB	1.05 (0.82, 1.33)	Low	1.01 (0.96–1.11)	Low

Quality of the evidence was rated based on GRADE methodology. Trials of direct comparison were rated down for presence of any of the following factors—risk of bias in literature, inconsistency, indirectness, imprecision, and publication bias. Quality of indirect estimates was initially derived from the lowest quality of first-order loops for direct estimates contributing to the indirect estimates. Quality of the network meta-analysis was derived from quality of combination of direct and indirect estimates and transitivity of trials. When moderate-high quality evidence was available from direct/pairwise estimates, they were used preferentially; when pairwise estimates provided only low or very quality of evidence or if there were no pairwise comparisons, then estimates from network meta-analysis were used to rate quality of evidence. None of the comparisons resulted significant

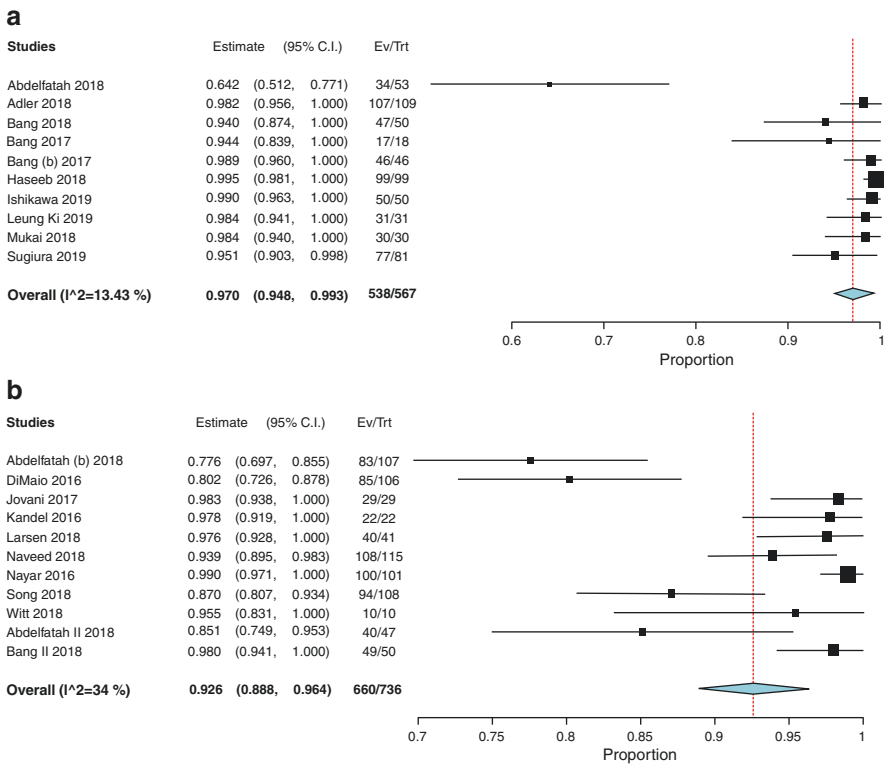

Fig. 5.2 Pooled analysis assessing rates of sample adequacy of (**a**) Franseen and (**b**) fork-tip fine-needle biopsy in targeting pancreatic lesions. Sample adequacy in targeting pancreatic masses was 95.6% (94–97.3%; I2 = 48.9%) with significantly higher rates of adequate samples obtained with Franseen needle (97%, 94.8–99.3% vs. 92.6%, 88.8–96.4%; $p = 0.006$)

However, the above cited network meta-analysis was unable to assess the performance of newer FNB needles due to the paucity of available RCTs, hence the aforementioned findings should be considered applicable mainly to ProCore® needle [59].

A recent meta-analysis of 24 studies performed by the same group specifically assessed the performance of newer needle designs in the diagnosis of solid masses [62].

As reported in Fig. 5.2, the two newer needles (Franseen and fork-tip) showed striking results in terms of sample adequacy (95.6%), rate of histological optimal core procurement (92.5%), diagnostic accuracy (95%), and sensitivity (92.8%) in pancreatic masses with no difference between the two different designs [62].

As expected, the aforementioned results were not influenced by the use of ROSE, a tool not routinely adopted in non-American centers, thus confirming that FNB may obviate to the need of an on-site pathologist to obtain optimal diagnostic outcomes [63].

Therefore, although current evidence do not seem to support a clear advantage of FNB over FNA for the management of pancreatic masses, newer biopsy needles are expected to influence the diagnostic algorithm of these lesions pushing the widespread use of EUS-guided biopsy in pancreatology [64, 65].

Of note, the single head-to-head trial directly comparing the two newer FNB needles did not report significant differences between the two devices [66], and this should represent a further research field in the future.

5.4 Pancreatic Cystic Lesions

In most centers, sampling of pancreatic cystic lesions (PCLs) involves the use of 19G or 22G FNA needles and an attempt to empty the cyst as much as possible with a single needle pass, in order to maximize diagnostic yield and minimize the risk of infection [64]. This approach, based on expert opinion, has never been adequately evaluated, and its effectiveness remains unproven.

Despite the large experience based on CEA or amylase dosage or the evaluation of the presence of mucus in the cystic fluid, none of these methods were proved to be able to accurately discriminate the type of lesion and the risk of malignancy [67–69]. In particular, major drawbacks of standard FNA are the relatively low sensitivity, reported to be as high as 54% in differentiating mucinous from non-mucinous cysts [67], and the difficulty in collecting adequate samples for biochemical analysis of the cystic fluid [70].

Targeted cyst wall puncture after aspiration of cyst fluid was shown to provide a specimen adequate for cytologic or cytologic/histologic evaluation in 65–81% of cases and to offer an additional incremental diagnostic yield for mucinous cyst of 29–37% over cyst fluid analysis/cytology alone [71, 72]. However, the diagnostic sensitivity of reverse-bevel FNB was disappointing in PCLs without solid components [71].

Recently, a through-the-needle microforceps device (Moray Microforceps®, US Endoscopy, Mentor, OH, USA) that can be passed through a standard 19-gauge EUS-FNA needle was developed for histologic sampling of PCLs. The main advantage of TTNB is to obtain adequate specimens retaining the stroma covered with the epithelial lining and, therefore, to preserve the histological architecture of the sampled tissue. These aspects allow ancillary techniques such as immunohistochemistry both on epithelium and on the stroma, thus improving the diagnostic and prognostic value of the technique [73]. Moreover, TTNB allows collecting adequate volumes of cystic fluid for both biochemical and molecular biology analysis and for cytology which can be associated with histology to improve diagnosis, as reported in several series [73].

There are currently 11 studies (excluding overlap series) assessing the diagnostic yield of TTNB in PCLs (alone or in comparison to standard FNA), showing a pooled sample adequacy rate of 85.3%, with diagnostic accuracy and sensitivity of 78.8% and 82.2%, respectively [74–84]. Available studies are reported in Table 5.5.

Table 5.5 Studies evaluating through-the-needle biopsy for sampling pancreatic cysts

Study	Country	Number of patients	Study period/ design	FNA cytology/ cyst fluid analysis	Lesion size (cm)	Main outcomes
Basar, 2018 [74]	USA	42	2015–2016/ retrospective	Yes	2.82 (1.2–6)	Adequacy: 90.5% Accuracy: 71.4%
Cheesman, 2019 [75][a]	USA	41	NR/ retrospective	Yes	3.7 (1.6–5)	Adequacy: 90.2% Accuracy: 68.3%
Crinò, 2019 [76]	Italy	61	2016–2018/ prospective	Yes	4.07 ± 1.42	Adequacy: 100%
Kovacevic, 2018 [77]	Multicenter	28	NR/ retrospective	No	3 (2.2–4.75)	Adequacy: 67.9% Accuracy: 67.9%
Mittal, 2018 [78]	USA	27	2016–2017/ retrospective	Yes	3.78 ± 1.69	Adequacy: 88.9% Accuracy: 77.8%
Robles-Medranda, 2019 [79][a]	Ecuador	36	2013–2018/ retrospective	Yes	NR	Accuracy: 83.3%
Samarasena, 2019 [80]	USA	15	NR/ retrospective	No	2.5 (0.48–3.9)	Adequacy: 86.7% Accuracy: 73.3%
Vestrup Rift, 2019 [81]	Denmark	27	2016–2017/ retrospective	No	3.5 (1.2–13)	Adequacy: 88.9% Accuracy: 88.9%
Zhang, 2018 [82]	USA	48	2016–2017/ retrospective	Yes	3.1 ± 1.1	Adequacy: 75%
Yang, 2019 [83]	USA	114	2016–2018/ prospective	Yes	3.51 ± 2.52	Adequacy: 83.3% Accuracy: 83.3%
Wilen, 2019 [84][a]	USA	30	2016–2018/ retrospective	Yes	2.73	Adequacy: 70%

FNA fine-needle aspiration
[a]Published as conference abstract

Therefore, TTNB seems to clearly outperform current available techniques for sampling pancreatic cysts; furthermore, the diagnostic performance of standard FNA is highly influenced by the presence of an expert pancreatic cytologist, who is not available in many centers. The TTNB technique may obviate to these problems by providing histological samples of the cyst wall including both the epithelium and

the stroma, an aspect particularly important in mucinous neoplasms characterized by the presence of an ovarian-like stroma [73].

However, in spite of the undoubted advantages of TTNB in comparison to FNA, diagnostic accuracy and sensitivity are still considerably inferior to solid pancreatic masses. In fact, it is possible to sample only the opposite wall of the cyst with respect to the point of entrance of the needle, and due to the uneven distribution of dysplasia inside the PCLs, there is a considerable risk of underestimating the real grade of dysplasia inside the cyst [73]. Moreover, some pancreatic cysts might have the so-called "denuded epithelium" [85], thus making it difficult to obtain adequate specimens even with a high number of passes.

While infectious adverse events related to EUS-guided sampling of solid pancreatic lesions are very rare [86], recommending against routine antibiotic treatment, prophylaxis with fluoroquinolones, or beta-lactam antibiotics is routinely used in the majority of studies on sampling of pancreatic cystic lesions; although this approach is based on long-standing clinical practice and very limited evidence, current guidelines recommend in favor of antibiotic prophylaxis when sampling PCLs [19].

The optimal choice of drug and dosage regimen has not been adequately studied. Most studies used an initial intravenous dose followed by oral administration for 3–5 days; however, there is limited evidence from two non-comparative studies that a single intravenous dose may be sufficient [87, 88]. However, two retrospective studies showed similar results in terms of infection rate between use and nonuse of antibiotic prophylaxis [89, 90]; therefore, this practice is likely to be reappraised in the forthcoming guidelines.

Sampling of PCLs raises some additional safety concerns regarding the risk of acute pancreatitis, in particular when the lesion is in communication with the main pancreatic duct. However, as reported in a recent meta-analysis [91], sampling of pancreatic lesions is safe although certain subgroups of patients are at increased risk (for example, cirrhotic patients) [92]. The role of pharmacological agents able to decrease the periprocedural risks of EUS-TA is still unknown, although statins showed interesting results in this regard [93].

5.5 Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is one of the novel imaging technologies that allows microscopic visualization of the mucosal surface epithelium. Optical biopsy at real time may further improve the diagnostic yield by reducing the sampling error [94, 95], thus obviating to the need of ROSE.

CLE has been in use for years in other fields of gastrointestinal endoscopy, such as in the differential diagnosis of gastric subepithelial or mucosal lesions or to assess Barrett esophagus [96]; in the last years, a new procedure called needle-based confocal laser endomicroscopy (nCLE), which involves a mini-CLE probe that can be passed through a 19-gauge needle during EUS-FNA, has been developed and tested in the clinical practice. This procedure allows the real-time visualization

of tissues at a microscopic level thus showing the potential to further improve the diagnostic accuracy of EUS-FNA, in particular in cystic lesions [97].

The main limitation of this technology is heterogeneity in histology, interobserver variability, reproducibility, need of pathologists and endoscopists for better interpretation, image quality, and sampling error [96, 97]. Therefore, further training and research are needed for applicability in real-time practice.

5.6 Conclusions

Important advancements in EUS-guided tissue sampling techniques and development of new needle designs have improved the diagnostic yield of both solid and cystic pancreatic lesions. This innovation in EUS has also opened the door for early diagnosis and precision therapy in the management of cancer patients. EUS-FNB is an invaluable tool, and newer FNB designs will probably play a pivotal role in the management of pancreatic lesions in the next future.

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Role of EUS Sampling in Pancreatic Cystic Lesions

6

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Key Points

- Pancreatic cystic lesions have a highly variable biological behavior, ranging from completely benign and non-evolutionary to invasive with metastatic potential.
- Currently no single examination allowing to obtain a precise diagnosis in all cases of pancreatic cystic lesions.
- Diagnosis is reached piecing together a puzzle of epidemiological, clinical, radiological, ultrasonographic, cytohistological, and cystic fluid analysis data.
- In this setting, cystic fluid analysis offers numerous possibilities to diagnose the type of lesion and evaluate its invasive potential.

6.1 Introduction

Over the last 20 years, there has been a dramatic increase in the use of cross-sectional imaging such as computed tomography (CT), magnetic resonance imaging, (MRI) and endoscopic ultrasound (EUS). This has resulted in the frequent detection of pancreatic cysts, incidentally identified in between 2% and 13% of cases [1, 2].

The vast majority of these lesions have an indolent course and will cause no issues to patients. However, a small subgroup can become aggressive, invading the pancreatic cyst wall and having a metastatic potential [3].

A single and unique diagnostic tool that can be effectively used in all pancreatic cystic lesions (PCL) is currently unavailable. Diagnosis is reached piecing together

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a puzzle of epidemiological, clinical, radiological, ultrasonographic, cytohistological, and cystic fluid analysis data.

The main information we require on PCL is basically twofold: what kind of cystic lesion are we dealing with? What is the probability that this lesion will require surgery?

The first point to emphasize with reference to diagnostic workup in patients with PCL is that the study of the pancreatic lesion can have an impact on patient management. It makes no sense to employ resources and expose the patient to investigations that will not modify his or her treatment. Therefore, patients considered too old, or with important comorbidities that would prevent surgery, should be excluded from this workup.

The number of different PCLs is considerable. However, the most common lesions encountered in routine clinical practice are: pseudocyst (PC), serous cystadenoma (SCA), mucinous cystic neoplasia (MCN), intraductal papillary mucinous neoplasia (IPMN), solid-pseudopapillary neoplasm (SPN), and neuroendocrine tumor (NET) with cystic degeneration.

In general, PCLs can be divided in two groups: those without evolutionary potential, PC and SCA, which therefore need minimal or no follow-up, and those with evolutionary potential. Among the latter, there is an indication for surgery for SPN, and usually for MCN, particularly if the lesion is larger than 4 cm in diameter and/or with mural nodules. Surgery is also indicated for IPMN involving the main duct, or for mixed-IPMN with main pancreatic duct >10 mm, jaundice, or mural nodules, or for IPMN of the branch duct (IPMN-BD) with "high risk stigmata," according to the International Association of Pancreatology (IAP) guidelines revised in 2017 [4]. On the other hand, patients with IPMN with "worrisome features" (see IAP guidelines) require further investigation. These patients are candidates for endoscopic ultrasound fine-needle aspiration (EUS-FNA) to assess the presence of morphological or cytological elements suggestive of advanced neoplasia (high-grade atypia or invasive neoplasia) according to the IAP and American College of Gastroenterology guidelines that, however, underline the importance of a multidisciplinary pancreatic team [5].

Although not specifically mentioned by the published guidelines, or included in their diagnostic algorithms, a number of investigations are available that can be performed on cystic fluid to help clarify the type of lesion and its evolutionary potential.

In this chapter, we review the most important and commonly used tests on cystic fluid and, in particular, mucus search, cytology, amylase, CEA, glucose, and molecular markers (Table 6.1).

6.2 Cytology of Cystic Fluid

The search for mucus on intracystic fluid aspirate should always be performed. Though only about 50% of mucinous pancreatic cystic lesions have considerable amounts of mucus in the cystic fluid, its identification is highly specific of mucinous

Table 6.1 Analysis of cystic fluid in the four most common cystic lesions of the pancreas

	Serous cystoadenoma	Mucinous cystoadenoma	BD-IPMN	Psudocyst
CEA				
• ≥192 ng/ml	±	++	++	±
• ≥5 ng/ml	+	+++	+++	++
• ≤5 ng/ml	+++	±	±	+
Amylase				
• >250 U/L	+	++	++/+++	+++
Glucose level				
• <50 ml/dl	–	+++	+++	++/+
Mucin	–	+	+	–
Cytology	Glycogen	Mucinous	Mucinous	Inflammatory
Molecular Marker	VHL	KRAS RNF43	KRAS GNAS RNF43	–
TP53/PIK3CA/PTEN CDKN2A/SMAD4	–	+++ (advanced cancer)	+++ (advanced cancer)	–

+++: very frequent; ++: moderately frequent; +: infrequent; ±: possible but very infrequent
BD-IPMN branch duct intraductal papillary mucinous neoplasm, *CEA* carcinoembryonic antigen

lesion. It is recommended to proceed with the smear in the endoscopy room or send the material to the laboratory "fresh" avoiding fixatives that could compromise the identification of mucus. Though mucin may be visible at aspiration, thick sheets of colloidal-like mucin covering much of the slides should be sought. This mucin allows for a diagnosis of mucinous cyst, even if acellular [6]. In lieu of viscosity, a "string test" has been suggested. This is done placing the fluid between the thumb and index, and gently pulling the two fingers apart. A cyst fluid that "strings" to 3.5 mm is considered mucinous. This test has a positive predictive value of 94% for diagnosis of mucinous cyst, but the negative predictive value is only 60% [7].

Cytology of cystic fluid through EUS-FNA is a fairly simple procedure, with a relatively low risk of complications. A large multicenter study on FNA in PCL showed a percentage of adverse events of 6%: 66.6% were mild complications and 33.3% moderate complications, and all cases resolved with medical therapy only [8].

Despite several published case reports of "seeding" during EUS-FNA of pancreatic lesions, previous studies have not clearly shown EUS-FNA increases the risk of tumor dissemination through the needle tract in pancreatic cancer [9]. With particular reference to PCL, the PIPE study on preoperative EUS-FNA of IPMN found no relation with increased frequency of peritoneal seeding in patients who underwent surgery [10].

However, although it has been proposed by several guidelines, not all agree with its use and it is not included in the diagnostic algorithms of some guidelines such as, for example, the European guidelines revised in 2018 [11].

The problem arises from the observation that cytology of cystic fluid, despite its high specificity, has a low sensitivity and is inadequate in a number of cases, which

can reach 50% or more [12], due to the low amount of cells dispersed in the cystic fluid, as highlighted by two meta-analyses [13, 14] and underlined by several guidelines [4, 5, 11]. A test used as a "rescue" in the presence of doubtful cases (with worrisome features or relative indications for surgery) seems inappropriate if it has excessively low sensitivity and adequacy, providing useful outcomes in an unacceptably low percentage of cases.

The new target appears to be the cystic wall (or, alternatively, the internal septa) where the cystic lesion cells are located. New tools including ultrasound-through-the-needle biopsy (EUS-TTNB) with microforceps (Morey™, US Endoscopy) through the 19-gauge needle and in vivo needle-based confocal laser endomicroscopy (*Cellvizio*®) have given encouraging results [15, 16], replacing or supporting cytology of the cystic fluid, and will certainly be considered when drafting new guidelines or reviewing existing ones. A more extensive discussion of EUS-TTNB is reported in the Chap. 4 of this book.

6.3 Amylase

Amylase levels in pancreatic cystic fluid are studied to understand if the cyst is communicating with the pancreatic duct or secondary ducts.

The most important use of amylases in cystic fluid is the exclusion of PC. Amylase values in PC are usually in the thousands, and almost never under 250 U/L [17–19]. Amylase values are elevated (usually thousands) in three-fourths of IPMN [18–20]. In serous cystoadenoma, the amylase value is usually less than 250 U/L, although there are a number of exceptions [17, 18, 21]. MCNs very rarely have macroscopic communication with the pancreatic duct; therefore, the expected level of amylase is low in pancreatic cystic fluid. However, several studies [17–19, 21] have shown amylase intracystic fluid levels in some MCNs can be elevated, with no particular differences between IPMN and MCN, most likely due to diminutive connections between the cyst and the ductal system.

6.4 CEA

Several tumor markers in PCL aspirate have been considered, such as carcinoembryonic antigen (CEA), CA 19-9, CA 72-4, and CA-125. CEA is considered the most accurate marker in differentiating mucinous from non-mucinous cysts, despite the continuous debate in literature on the best cutoff value. Cutoff ranges from 20 ng/mL to 800 ng/mL in various studies, with greater sensitivity for lower ones and greater specificity for higher ones. However, the most frequently utilized cutoff derives from a large prospective study by Brugge et al. [22] on 112 patients who underwent surgery. This study established that a level ≥192 ng/mL has a diagnostic sensitivity of 75%, a specificity of 84%, and an accuracy of 79% in differential diagnosis of mucinous and non-mucinous cysts. In another pooled analysis from 12

studies, a value >800 ng/mL reached a specificity of 98%, but a sensitivity of only 48% [17].

Very low values of CEA can also be useful. CEA levels lower than 5 ng/mL have been found in a pooled analysis of published studies [17] to be highly diagnostic for SCA or PC (sensitivity 50%, specificity 95%). A retrospective analysis [18] of patients with histologically confirmed diagnosis of pancreatic cysts showed that intracystic fluid CEA less than 5 ng/mL for a diagnosis of non-mucinous lesions had a sensitivity of 44%, a specificity of 96%, and a diagnostic accuracy of 78%. In fact, very few mucinous cysts have values below 5 ng/mL [18, 20]. However, for PC there are more widespread values: rarely they exceed 192 ng/mL (5–14%), and only 25% have a value of less than 5 ng/mL [18, 23]. In a study on 21 PC, the median of intracystic fluid CEA was 41 ng/mL (mean 129 ng/mL), therefore with significantly higher levels compared with SCA [24].

More recent studies have reduced the usefulness of intracystic CEA to distinguish mucinous from non-mucinous lesions. A large multicenter study on 226 patients undergoing pancreatectomy estimated a cutoff value of 192 ng/mL yielded a sensitivity of 61%, and a specificity of 77% differentiating between mucinous and non-mucinous cystic lesions, and would misdiagnose 39% of mucinous cases [23]. In the same study, although values below 5 ng/ml seem quite specific for SCA, despite median CEA levels for serous cysts found to be 1.7 ng/mL, 31% of serous cysts would have been misclassified when using a cutoff of 5 ng/mL.

Moreover, it has been established that the accuracy of CEA in differentiating between benign and malignant pancreatic cysts is poor. This limitation was highlighted by several studies [18, 22, 25] and by a meta-analysis by Ngamruengphong et al. [26].

Another limit of intracystic CEA measurement is that the high viscosity of some PCL prevents aspirating a sufficient amount of cystic fluid (approx. 0.5 ml) to perform CEA testing, with up to 50% of cases reported by de Jong et al. in their European multicenter study [12]. Furthermore, it is worth remembering how in some cases CEA levels can be elevated (≥192 ng/ml) in other PCL, such as PC, lymphoepithelial cysts (frequently), retention cysts, and, in rare instances, SCA.

Finally, a recent study highlighted the variability of intracystic CEA at repeated sampling [25]. In fact, CEA changed in about 20% at repeated EUS-FNA without any significant modification of features.

All these limits of CEA measurement in PCL fluid underline the need to interpret this test cautiously, and to never rely on it alone to make a decision about the patient, using it instead in conjunction with the other available information.

The other tumor markers (CA 72-4, CA 125, CA 19-9, and CA 15-3) studied in cystic fluid from PCL have no role in clinical practice [17, 22].

6.5 Glucose

The use of glucose levels has recently been suggested as a useful cyst fluid marker to distinguish between mucinous and non-mucinous cysts.

In 2013, Park et al. [27], who were looking for potential cyst fluid markers for pancreatic mucinous cysts, were the first to note that glucose levels were significantly lower in mucinous cysts compared to non-mucinous cysts (5 vs. 82 mg/dL, $P = 0.002$). Using a cutoff of 66 mg/dL, they found a sensitivity, specificity, and diagnostic accuracy of 94%, 64%, and 84%, respectively.

The same group, in 2015, in a subsequent study [28] on patients undergoing surgery, lowered the cutoff of intracystic glucose to <50 mg/dL, finding a sensitivity and specificity for the definition of mucinous cysts of 88% and 78%, respectively, using glucometer, 95% and 57% using laboratory glucose, and 81% and 74% using reagent strip glucose. In the same study, the CEA cutoff >192 ng/mL for mucinous cysts had a sensitivity and specificity of 77% and 83%, respectively.

In 2018, Carr et al. [29] proposed a prospective study comparing intracystic fluid glucose with a threshold ≤50 mg/dL and CEA with a threshold >192 ng/mL, in samples from 153 patients with pathologically confirmed diagnoses. Sensitivity, specificity, and accuracy for mucinous cysts were, respectively, 92%, 87%, and 90% for glucose, and 58%, 96%, and 69% for CEA. Combining glucose and CEA (positive test defined as any one positive single test) to differentiate pancreatic mucinous cysts from non-mucinous, they found a sensitivity of 95%, a specificity of 85%, and a diagnostic accuracy of 93% ($P = 0.03$).

In 2019, a study by a Portuguese group [30] confirmed the previous results, obtaining a sensitivity and specificity for glucose <50 mg/dL for diagnosis of mucinous cyst of 89% and 86%, respectively, and with CEA >192 ng/mL, a sensitivity of 72% and a specificity of 96%.

The median glucose levels were 5 mg/dL in two studies evaluating mucinous cystic lesions [27, 28]. On the other hand, the median glucose levels ranged between 86 and 103 mg/dL in studies evaluating SCA [27, 29]. One important aspect to highlight is that PCs often present glucose levels below 50 mg/dL [28, 30]. In a study by Zikos et al., the median glucose level in PCs was 42 mg/dL using glucometer and 21 mg/dL using laboratory glucose. In these cases, CEA could help for differential diagnosis [28].

This seems to indicate intracystic glucose levels can effectively discriminate mucinous lesions from non-mucinous lesions, similarly or even more accurately than CEA, with which it can be associated and compared to obtain a more reliable diagnosis.

Though one study [29] reported that blood glucose levels on the day of the collection appears to not correlate with cyst fluid glucose levels, this will need to be confirmed by future studies.

However, the intracystic glucose level is very easy to identify, even on-site during EUS with a glucometer (although glucometers do not read low glucose levels, usually below 30 mg/dL, so these samples must be sent to the laboratory). This is an inexpensive process requiring a minimum amount of fluid (<2 μL) for the glucometer versus laboratorial glucose and CEA assays requiring 50 μL and 200 μL, respectively. This can be useful in PCL with small amounts of cystic fluid available for performing tests. However, in some mucinous cysts, the high viscosity can preclude glucose reading using a glucometer (in about 10% of cases) [30]. Furthermore, intracystic glucose, like CEA, also has no role in discriminating benign from malignant lesions.

6.6 Molecular Markers

The advent of next-generation sequencing has resulted in a faster and more effective sequencing method than the previously available ones. Over the past few years, several studies have sequenced DNA isolated from cystic epithelial lining and cyst fluid to reveal recurrent genetic alterations specific for pancreatic cyst type, and the likelihood of progression to pancreatic ductal adenocarcinoma (PDAC) [31–38].

At present, we can obtain diverse and useful information not only to distinguish different types of PCL but also to assess the risk of advanced neoplasia (high-grade dysplasia and invasive adenocarcinoma).

The most frequent genetic alteration in IPMN is an oncogenic KRAS mutation, present in 80% of cases. This mutation is not associated with the grade of dysplasia. A somatic mutation in the GNAS oncogene is seen in 65% of IPMN [37, 38]. One of these two mutations is present in more than 96% of IPMN, and both are considered early genetic events in the progression to PDAC [32]. The third observed mutation is an inactivating mutation in the tumor suppressor gene RNF43, seen in 14–38% of IPMN, with frequent loss of heterozygosity [32, 35].

All other mutations in suppressor genes, such as TP53, PIK3CA, PTEN, CDKN2A, SMAD4, and TP53, occur late in the neoplastic progression of IPMN and are associated with advanced neoplasia [32, 37, 38].

Similarly to IPMN, KRAS mutations are the most common findings in MCN [32, 37, 38], but conversely from IPMN, in MCN their prevalence increases with the degree of dysplasia. Jimenez and colleagues [39] detected KRAS mutations in 26% of low-grade MCN, and in 89% of MCN with advanced neoplasia. RNF43 alterations are also present in MCN, with a prevalence of 8–35%. Like IPMN TP53, PIK3CA, PTEN, CDKN2A, and SMAD4 are detected in MCN with advanced neoplasia. By contrast with IPMN, GNAS mutations are always absent in MCN [32, 35].

The only genetic mutation in SCA is in tumor suppressor gene VHL, which has been found in 75–100% of SCA [32, 35, 36]. A subset of patients with von Hippel-Lindau disease, associated with germline mutations in VHL, develops multiple SCA throughout the pancreas.

In 2017, it was noted that vascular endothelial growth factor (VEGF)-A is very elevated in SCA fluid. In fact, the genetic alteration that inactivates tumor suppressor VHL can result in upregulated VEGF-A expression. VEGF-A alone has a 100% sensitivity and an 83.7% specificity for distinguishing SCA from other PCL with a threshold set higher than 5000 pg/mL [40]. If confirmed by future studies, this biomarker could be used to support or exclude a diagnosis of SCA.

SPN was found to have a single mutation in the CTNNB1 gene [32, 35]. Mutations in TP53 and PIK3CA have also been described in SPN; however, these are rare findings [35].

No genetic alterations have been reported in pseudocysts, lymphoepithelial cysts, and squamoid cysts of the pancreas [36, 38].

In 2018, in a large study on DNA-based testing of pancreatic cyst fluid in 595 patients, 626 pancreatic cystic fluid specimens were obtained by EUS-FNA and assessed by targeted NGS. The study showed that:

- KRAS/GNAS mutations have a sensitivity of 89% and a specificity of 100% for mucinous lesions.
- GNAS mutations with mutant allele frequency (MAF) >55% or combinations of KRAS/GNAS mutations associated with alteration in PT53/PIK3CA/PTEN have an 89% sensitivity and 100% specificity for advanced neoplasia.
- Other worrisome features, such as ductal dilation and mural nodules, but also malignant cytopathology had lower sensitivity (42%, 32%, 32%) and specificity (74%, 94%, 98%) [38].

A paper was recently published on gene mutations in cystic fluid associated with clinical features, imaging characteristics, and cyst fluid biochemical markers and integrated using supervised machine learning techniques to develop a comprehensive test called CompCyst. The study also incorporated loss of heterozygosity and aneuploidy. The authors found that clinical management informed by the CompCyst test was more accurate than the management dictated by conventional clinical and imaging criteria alone. Furthermore, application of the CompCyst test would have spared from surgery more than half of patients who underwent unnecessary cyst resection [41].

Molecular markers seem particularly interesting in the workup of PCL as they indicate both the type of lesion and its malignant evolutionary potency. If future studies confirm the described results, they could completely change the approach to these lesions.

6.7 Other Biomarkers

Other promising biomarkers are under evaluation: different gene mutations, such as BRAF, hTERT, STK11, BRC1, DNA methylation in genes, micro-RNAs, but also different biomarkers such as neutrophil-to-lymphocyte ratio in blood or cyst fluid cytokines and prostaglandins [42, 43]. While all have shown promising results, we are waiting for results of current studies to identify the most promising clinically relevant biomarkers and to target analyses for further development.

An alternative suggested approach is to analyze molecular markers in pancreatic fluid collected from the duodenum, which could avoid the potential adverse events of direct sampling of pancreatic fluid using FNA. In addition, pancreatic fluid can contain alterations present in multiple cysts throughout the pancreas, rather than a single cyst [44, 45].

Future studies will identify the ideal biomarkers for PCL. These markers will help predict malignant potential and should be easily obtained, widely applicable, and inexpensive. Also, as previously reported [42], these will likely be a conglomerate of the current known biomarkers.

6.8 Conclusion

Cystic lesions of the pancreas continue to represent a clinical challenge, leading to high costs for diagnosis and, above all, follow-up. Diagnosis is currently based on clinical data, radiological techniques, and studying the cystic fluid and cystic wall. While we are aware that cytological diagnosis of cystic fluid has considerable limitations in terms of sensitivity and adequacy, the study of the cystic walls seems to offer better opportunities, both with the microforceps and endomicroscopy. These, however, have not yet been included in the diagnostic algorithms of the published guidelines, since information on their effectiveness and safety are not definitive. In this sense, cystic fluid analysis is still widely used worldwide. New cystic fluid tests such as glucose and, above all, molecular biology have produced very interesting results, and it is likely that they will change the approach to these lesions in the very near future.

Several new biomarkers have showed promising results, and we are waiting for results of new studies to identify the most clinically relevant biomarkers and to target analyses for further development.

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Endoscopic Ultrasound-Guided Drainage of Pancreatic Fluid Collections

7

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7.1 Background

Pancreatic fluid collections (PFCs) are inflammatory in nature and usually arise as a complication of acute pancreatitis (AP) or chronic pancreatitis and less commonly are iatrogenic or due to other causes including blunt trauma [1, 2]. Per the Revised Atlanta classification, these PFCs are divided based on the character of inflammation, wall maturity, and timing (>4 weeks). Consequently, majority of these PFCs like acute pancreatic fluid collection (APFC), which develop as a local complication of mild to moderate interstitial edematous pancreatitis (IEP), may resolve spontaneously [3]. In some cases, it can progress to form an organized encapsulated collection known as pseudocyst which may also regress with conservative management [4]. These pseudocysts, in few instances, can become symptomatic leading to infection, abdominal pain, gastric outlet obstruction, and obstructive jaundice. Clinically significant PFCs can also develop as a sequalae of severe AP with or without necrosis [5]. These can evolve into an organized collection of necrotic material called walled-off pancreatic necrosis (WOPN) Table 7.1.

Multiple strategies including open surgical drainage, percutaneous drainage (PD), and endoscopic drainage are used in the management of PFCs. Current clinical practices favor use of EUS-guided drainage (EUS-GD) of these collections mostly because of the minimally invasive technique, fewer adverse events, increased effectiveness, low morbidity and mortality, and high clinical success [6–8]. Shorter

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Table 7.1 Summary of features of pancreatic fluid collections

Type of PFC	Time of development	Encapsulated	Necrosis	Endoscopic drainage
Acute pancreatic fluid collection	<4 weeks	No	No	No
Acute necrotic collection	<4 weeks	No	Yes	No
Pseudocyst	>4 weeks	Yes	No	Yes. EUS-GD
Walled-off necrosis	>4 weeks	Yes	Yes	Yes. EUS-GN

EUS-GD endoscopic ultrasound-guided drainage, *EUS-GN* endoscopic ultrasound guided-necrosectomy

hospital stays, lower reintervention rate, and less need of follow up imaging favor EUS over PD [9, 10]. However, some complex patients with extensive collections extending into the paracolic gutters may require a combined approach.

7.2 Indications of Drainage

Endoscopic management of PFCs by any approach requires few prerequisites for a successful intervention. Drainage of PFCs endoscopically requires it to a have mature wall and is performed usually after 4 weeks of the development of PFC [11]. Although, there is recent evidence that earlier (<4 weeks) endoscopic drainage is feasible as long as the wall is well formed [12]. Encapsulation of these collections is essential in complete resolution of the PFCs apart from reducing the post-procedure adverse events [13]. These collections have to be in close proximity to the gastro duodenal wall preferably <1 cm for effective visualization and drainage, thereby decreasing the risk of perforation, stent migration, and bleeding. The site of the cyst in the pancreas does not correlate with treatment outcomes [14]. Majority of the APFC resolve spontaneously, and around 10–20% develop into pseudocyst or evolve into necrosis, which are clinically significant. On the other hand, acute necrotic collections (ANCs) have a higher rate of progression to a WOPN, around 50%. Time interval from APFC to resolution or development of a pseudocyst and ANC to a WOPN is crucial in deciding the management including conservative vs. drainage and has direct impact on mortality and clinical success of the intervention [15].

Current referendum is mostly on the drainage of clinically symptomatic collections. A PFC causing symptoms of significant abdominal pain, gastric outlet obstruction (GOO) (Fig. 7.1), biliary obstruction, infection is eligible for drainage regardless of the size (Fig. 7.2) [11]. Certain spontaneous complications with PFCs including hemorrhage and infections increase the risk of mortality [12]. Decision to drain these PFCs should be made after multidisciplinary dialogue and comprehensive consideration of the risks and benefits of the intervention.

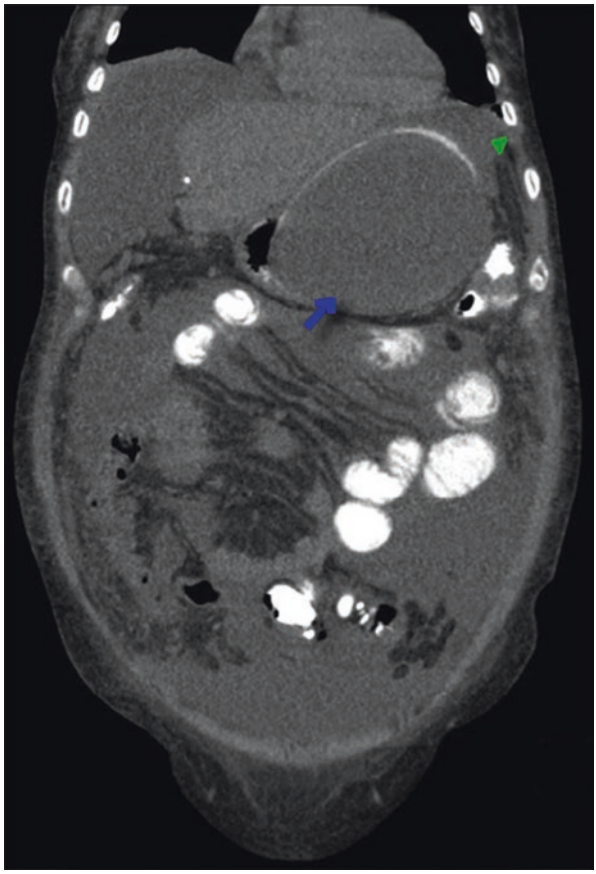

Fig. 7.1 Large pseudocyst (arrow) compressing the stomach (arrow head) and causing gastric outlet obstruction (GOO)

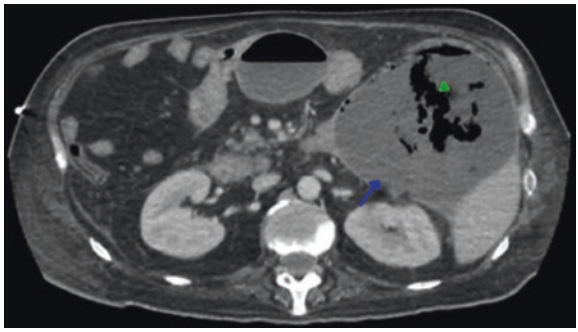

Fig. 7.2 Large infected PFC (arrow) with internal gas (arrow head) on CT scan

7.3 Evaluation for Drainage

Patient selection and timing of the intervention are important determinants of clinical outcomes of the procedure. Delayed intervention on a well-encapsulated collection is associated with lower mortality [16]. Pre-procedural radiographic cross-sectional imaging studies provide sufficient information to plan the timing of intervention. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the widespread imaging modalities utilized in these scenarios. These cross-sectional imaging studies provide vital information regarding maturity of the wall, location and size of the PFC, and amount of solid debris or necrosis (Fig. 7.3).

CT is one of the widely used imaging study in the evaluation and management of patients with AP. Multivariate analysis of a prospective study identified that the degree and presence of peripancreatic necrosis predicted the development of infected pancreatic necrosis; whereas trans parenchymal necrosis with upstream viable pancreas and no peripancreatic necrosis were associated with pseudocyst development [17]. Differentiation of a pseudocyst from a WOPN with help of contrast-enhanced CT (CECT) is helpful in planning the appropriate therapeutic intervention [18, 19].

Despite the above advantages, CT scan can significantly underestimate the amount of necrosis present in the PFC as compared to MRI and EUS [20]. Other adverse effects of CT scan including ionizing radiation exposure and iodized contrast administration leading to kidney injury can be avoided with the use of MRI. Conventional MRI can help in assessing solid debris with higher sensitivity and specificity than CECT [21]. Diffusion-weighted MRI was found to have higher sensitivity in finding presence of infection as compared to conventional MRI and CECT [22, 23]. Pancreatic duct disruption can be better visualized in the MRI [24]. Abdominal ultrasound (US) serves as noninvasive, cheap, and widely available modality to monitor PFC after an episode of AP. It is noted to have a comparable accuracy as MRI/EUS [25], although the results are very operator dependent. Other

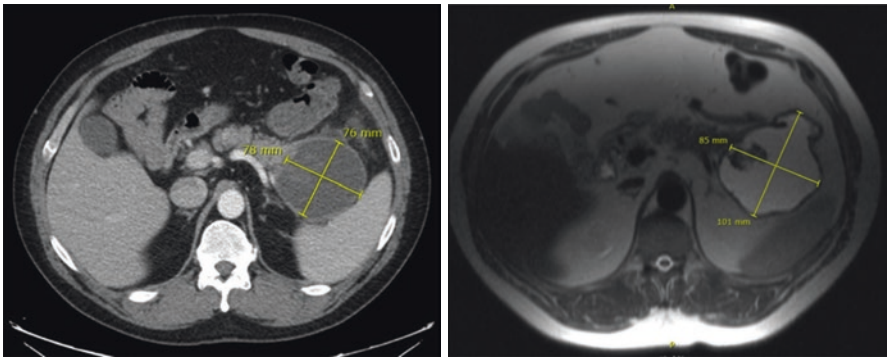

Fig. 7.3 Walled-off pancreatic necrosis (WOPN) in the tail of the pancreas shown on CT scan (left) and on MRI (right)

limitations of US include lack of information pertaining to the collaterals around WOPN and carries low sensitivity in characterizing collections with high solid content and air. Therefore, it has largely fallen out of favor as an investigative imaging modality in patients with PFC.

One cannot stress the importance of detailed history, physical examination, and review of laboratory studies for appropriate patient selection. Not surprisingly, higher mortality was associated with invasive surgical drainage in complex patients with poor cardiac and performance status. This resulted in shift of pendulum towards minimally invasive techniques like EUS-GD. Pre-procedure optimization of platelet count >50,000 and INR <1.5 is an important prerequisite to avoid complications associated with bleeding. Medications like antiplatelets and anticoagulants should be withheld by careful assessment of thromboembolic risk and bleeding risk [26]. Routine antibiotic prophylaxis is not recommended for infection prevention in PFC according to AGA and ESGE guidelines [27, 28].

7.4 Equipment

These procedures are performed at centers with appropriate interventional and surgical support. Advanced endoscopist with an adequate expertise in the intervention [29] performs the procedure under general anesthesia or deep sedation [11, 30]. Routine monitoring of patient's vital signs, pulse oximetry, and capnography for patients undergoing deep sedation is recommended.

Carbon dioxide is a safe alternative used for insufflation instead of air to minimize the risk of gas embolism [31]. CO_2 is rapidly absorbed by the mucosal lining and tissue and exhaled by lungs thus decreasing the risk in an event of gas embolization in higher risk endoscopic interventions [32]. Various randomized controlled trials have demonstrated improved post-procedural pain and abdominal distention with CO_2 insufflation [32, 33].

7.4.1 Echoendoscope

Endoscopic ultrasound, like any other ultrasound, utilizes the same technique of processing reflected or refracted sound waves by the transducer to generate an image. Resolution of the image depends upon the number of piezoelectric crystals used in the transducer and frequency emitted. Higher frequencies provide higher resolution images of objects at a closer distance <2 cm and lower frequencies with better penetration provide images up to12 cm [34]. Two major echoendoscopes are radial and curved linear array (CLA) which are used for luminal imaging and therapeutic interventions, respectively [35].

Oblique viewing CLA echoendoscopes have remained the standard of practice for the use of therapeutic interventions for many years. Recent advancements in technology have delivered forward viewing CLA [36] with similar clinical success,

ease, and safety [37, 38]. Forward viewing CLA is noted to have longer time to the initial puncture however, thereafter, a decreased time to placement of stent was noted [37]. Larger diameter of working channel of these echoendoscopes 3.7/3.8 mm allows passage of therapeutic tools like a larger diameter stent.

7.4.2 Stents

Various types of stents are used in maintaining the patency of the cystoenterostomy fistula tract. Size, shape, material, and technology of the stent significantly affect the drainage, stability, and clinical resolution of the PFC. Historically, plastic pig-tail stents have been widely used for drainage of PFCs (Fig. 7.4). These stents have proven technical and clinical success for the drainage of smaller, uncomplicated pseudocysts [39–41]. As per the AGA and ESGE, long-term indwelling plastic stents are preferred in PFCs associated with disconnected pancreatic duct in high surgical risk patients [41–43]. However, these stents were noted to have several disadvantages mostly due to its size and narrow lumen (7–10 F) for drainage. These are shown to be less effective in drainage of PFC with solid debris/necrosis [14] due to their prompt occlusion leading to infection and need for repeat endoscopic reintervention. Use of multiple stents in order to effectively drain a larger PFC is also time consuming. Migration and malemployment of these stents are other reasons which have made them fall out of favor [44]. These drawbacks led to the use of larger caliber metal stents for drainage of PFCs especially WOPN.

SEMS (self-expanding metal stents) (Fig. 7.5) are fully covered stents which have been widely used and have proven their efficacy, largely attributed to their larger diameter, in the drainage of pseudocyst, and WOPN [45–47]. A recent meta-analysis evaluated 905 patients from seven studies and showed that metal stents are superior to plastic stents with a clinical success of 94.1% compared to 82.6%,

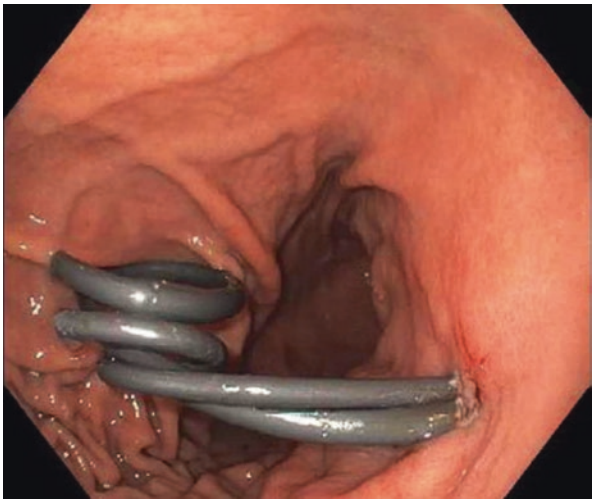

Fig. 7.4 Endoscopic view of a plastic stent for the drainage of a pseudocyst

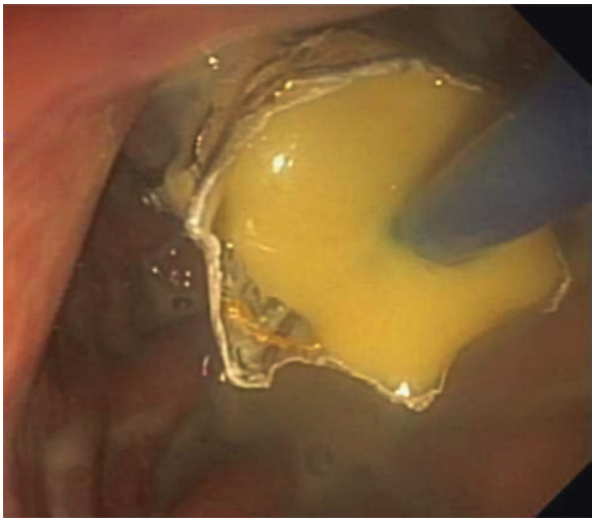

Fig. 7.5 Endoscopic view of pus flowing from SEMS placed for infected PFC drainage

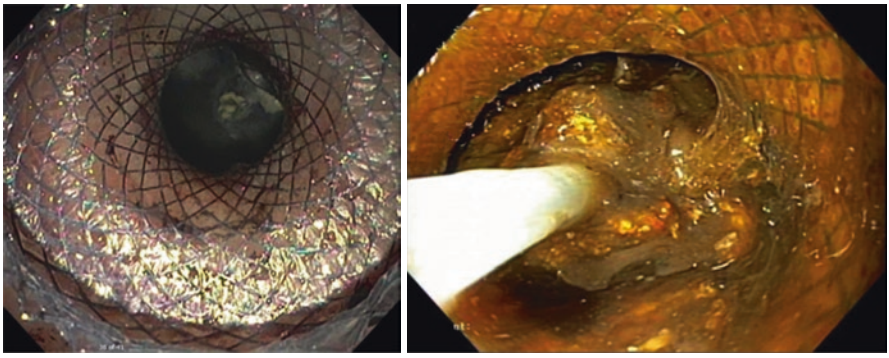

Fig. 7.6 Endoscopic view of LAMS, which provides a larger entry channel to the PFC cavity (left) and allows for serial direct endoscopic necrosectomy (right)

respectively. This meta-analysis had 5 out of 7 studies that used dedicated lumen apposing metal stent (LAMS). Metal stents were also reported to have lower adverse events however no statistically significant difference was noted in the stent migration and bleeding rates in both groups [47]. Major advantage of the metal stents over plastic stent is in the drainage of WOPN as it provides a larger channel for egress of necrotic debris and for serial access for direct endoscopic necrosectomy (DEN) (Fig. 7.6). The number of endoscopic procedures needed for successful management of PFCs was significantly lower with LAMS as compared to SEMS and plastic stents [48]. Despite these advantages over plastic stents, SEMS are associated with delayed complications including risk of bleeding, superinfection, and migration of the stent [45, 49]. Transluminal stent with lumen apposing properties or LAMS (Fig. 7.7) was first utilized by Binmoeller and Shah [50]. An AXIOS (Xlumena Inc., Mountain View, CA, USA) is a dumbbell-shaped 15 mm and 20 mm diameter,

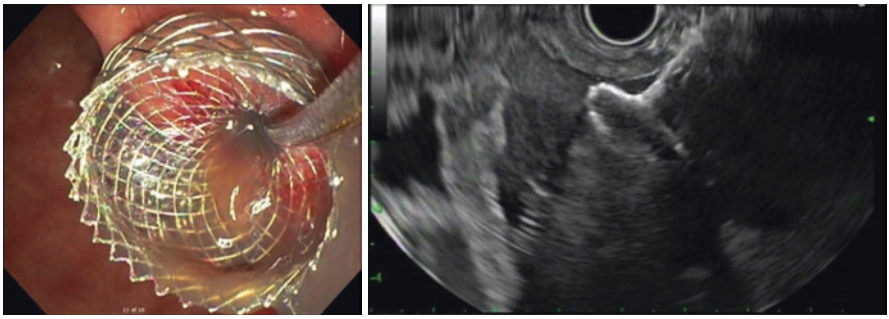

Fig. 7.7 Endoscopic view of the proximal end of LAMS (left) and endosonographic view of the distal end of LAMS (right) that was placed through the stomach for PFC drainage (i.e., EUS-guided cystgastrostomy)

Table 7.2 Types of stents commonly used with EUS-guided drainage

Stents	Manufacturer	Size	Properties	Image
AXIOS	Xlumena Inc., Mountain View, CA, USA	Lumen diameter—6 mm, 8 mm, 10 mm, 15 mm, 20 mm. Flange diameter—14 mm, 17 mm, 21 mm, 24 mm, 29 mm, resp	Braided nitinol wire and fully covered Double-walled flanges perpendicular to stent for wall apposition	
Spaxus	Niti-S Spaxus stent (Taewoong Medical Co., Ltd., Ilsan, Korea)	Lumen diameter—8 mm, 10 mm, 16 mm. Length—20 mm. Flange diameter—25 mm	Nitinol wire and fully covered silicone membrane Flanges fold back for wall apposition after deployment	
NAGI	(Taewoong-Medical Co.)	Lumen diameter—10 mm, 12 mm, 14 mm, 16 mm Length—10 mm, 20 mm, 30 mm Flared flanges of 20 mm diameter	Suture attached to the end to prevent migration	
Aixstent	(Leufen Medical, Aachen, Germany)	Lumen diameter—10 mm, 15 mm, 25 mm Length—30 mm	Fully covered wide flanges atraumatic folded-wire flanges to prevent tissue damage from the ends of the stent Available only in Europe	

10 mm and 15 mm length and is cautery (HOT AXIOS) and non-cautery (COLD AXIOS) enhanced stent. The HOT AXIOS is deployed in single-step thereby significantly reducing the duration of the procedure [51, 52]. Other commonly used LAMS outside the United States are Spaxus, NAGI™, and Aixstent [53] (Table 7.2).

7.4.3 Accessories

Cystotomes are the commonly used access devices for transluminal puncture when placing a stent other than cautery-enhanced LAMS. The cystotome cyst enterostomy knife (Cook Medical, Inc) comprises of a 5 F, 190-cm inner catheter with a removable 0.038-inch needle-knife electrode advanced to its tip, housed within a 10 F, 165-cm outer catheter that has a diathermic ring electrode at its distal end. Several commercially available 19G FNA needles are used for EUS-guided puncture followed by a 0.025-inch or a 0.035-inch guidewire passage [54]. Single-use longer (>450 cm) guidewires are used in most of EUS interventional procedures. Tract dilatation can be performed using balloon dilators, guidewire catheters [55], or cystotomes and needle-knife sphincterotomes [56].

7.5 Technique

7.5.1 Drainage of Pseudocyst

Endoscopic management of the pancreatic fluid collections has changed over the time. Historically, endoscopic drainage of PFCs via a transmural approach was used. This approach identified an area of maximal bulge in the gastric wall and gained access at the site under flouroscopy. This technique was predisposed to higher risk of perforation, bleeding, or tissue injury. Hence, EUS with its larger accessory channel for therapeutic intervention and ability to provide real-time transmural visualization of PFC during drainage is considered first-line endoscopic therapeutic modality for drainage of PFCs (Fig. 7.8a, b) [57].

In "Seldinger technique," an oblique/forward viewing linear array echoendoscope is advanced into the stomach or duodenum. PFC and surrounding structures including blood vessels are visualized under doppler. A puncture site in close approximation to PFC is identified and a 19G access needle is inserted. Stylet is drawn out and guidewire is advanced through the lumen of the needle under fluoroscopic guidance after contrast instillation and/or aspiration of cyst contents. Dilatation of the tract utilizing catheters, cystotomes, and balloon dilators is performed [58]. Various methods of drainage are utilized including insertion of plastic stents, nasogastric drainage of fluid, and placement of SEMS or LAMS. A stent is advanced over the guidewire to form a tract for drainage. This is followed by an optional step of balloon dilation of SEMS or LAMS lumen if same session DEN is planned. Success is measured usually as technical success (correct deployment of the stent into the cavity) and clinical success (resolution of symptoms and PFC) which marks resolution. Various studies have reported good clinical and technical success rates ranging 90% and beyond [55, 59–63].

Development of Hot AXIOS stent and electrocautery-enhanced delivery system (EC-LAMS) has facilitated and integrated the multistep process. This system allows the puncture and release of the stent in one step. This was first described clinically by Binmoeller and Lau et al. [64]. Delivery system combines an access catheter

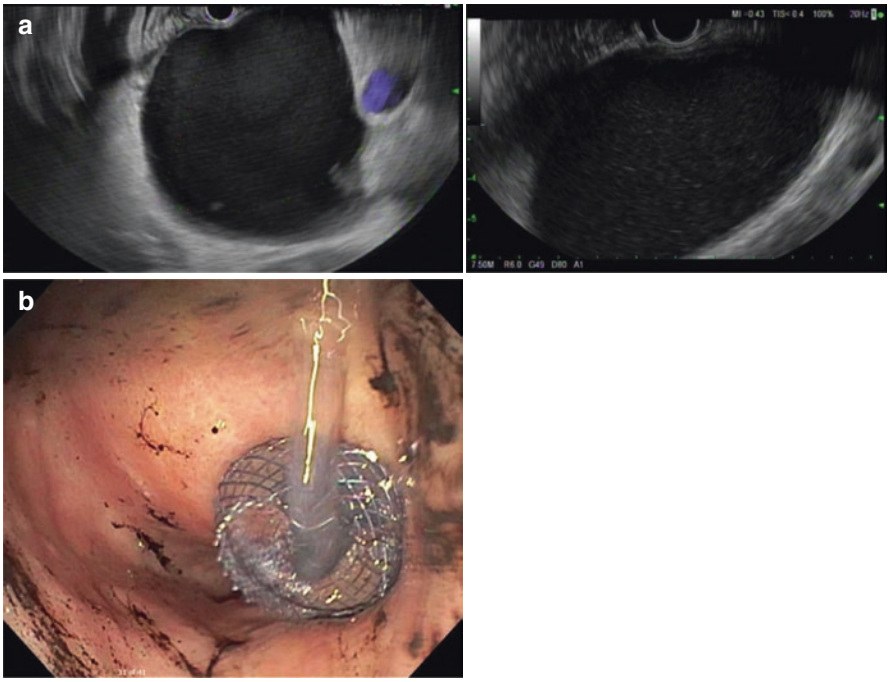

Fig. 7.8 (**a**) Large pseudocyst on endoscopic ultrasound (EUS) views. (**b**) Endoscopic view of the stomach after placement of lumen apposing metal stent (LAMS) and clear fluid draining out the pancreatic pseudocyst

which is enabled with a cautery tip and LAMS. It utilizes trans gastric or trans duodenal approach for PFCs drainage. Once the site is identified under EUS and endoscopic guidance, electrocautery is unlocked and activated using the diathermy pedal. It is advanced steadily while avoiding any vital structures and blood vessels. Distal flange is passed initially across the cystic wall while creating an apposition between two lumen walls followed by proximal flange towards gastric/duodenal wall. This single-step system significantly reduces the time of the procedure, hence potentially limiting the complications related to procedure. Yoo et al. described 100% technical and clinical success in patients with PFCs and no procedure-related complications [65]. A larger retrospective study [66] proved EC-LAMS as safe and effective modality to use with only 5 out of 93 patients showing major adverse events. It is generally recommended to remove the LAMS within 4 weeks of placement; however, expertise of clinician guides the timing at this point.

7.5.2 Drainage of WOPN

Patients with necrotizing pancreatitis who have inadequate response to conservative management, including drainage or develop infected necrosis not responding to

antibiotics, require further intervention. Necrosectomy is indispensable in these patients due to higher chances of morbidity or mortality and risk of infection and severe sepsis in such patients. However, open necrosectomy (ON) is associated with perioperative risks, increased recovery, long-term complications of surgical procedure, and mortality as high as 10–27% [67]. As compared to ON, minimally invasive surgical approach including laparoscopic and video-assisted retroperitoneal debridement (VARD) or direct endoscopic necrosectomy (DEN) (step-up approach) is associated with lower risk of death [68]. DEN initially reported by Seifert et al. [69] gained widespread clinical interest after it showed promising clinical success by Seewald et al. [70]. It has shown reduced mortality and other major complications of fistula formation, dissemination and seeding of infection, reduced hospital stay and cost as noted in TENSION trial [71–73]. That said, DEN serves as a preferred approach for treatment due to higher initial clinical success, lower recurrence rate, and reduced incidence of multi-organ dysfunction [11, 74].

PANTER trial compared a total of 88 patients randomly assigned to minimally invasive step-up approach to surgical open necrosectomy. Major complications were noted to be more common in open surgical approach with a significant difference of new onset multi-organ failure in two groups. Other significant results included lower health care costs, ICU admissions with step-up approach [75]. Another controller assessor-blinded PENGUIN clinical trial randomized 22 patients and showed similar results with lower new-onset multi-organ failure, decreased pancreatic fistulas and proinflammatory response as well as composite end point as compared to open necrosectomy [74].

A recent multicenter randomized superiority trial noted similar findings of non-inferiority to the surgical step-up approach and lower complications rate [7]. DEN is performed if the conservative management has failed and when higher level of necrotic solid debris is not accessible with standard drainage techniques. Initial steps or technique remains similar when an EUS is required to visualize a WOPN (Fig. 7.9a). Access into the cavity is gained and usually a larger bore stent such as a SEMS or most commonly nowadays an LAMS (Fig. 7.9b). Dilatation of the stent lumen is sometimes required to facilitate passage of endoscope (Fig. 7.9c). It is followed by irrigation and aspiration of the debris by suctioning or use of accessories like Dormia baskets, snares, and retrieval nets (Fig. 7.10a). A novel morcellator device recently used allowed complete resolution of the WOPN with 80% solid necrotic material resulting in successful debridement and liquefaction [76]. Gentle debridement is crucial to avoid complications including bleeding. Stents can be left in place for repeated access and continued drainage until WOPN cavity is cleared from necrotic material (Fig. 7.10b) [77].

Various multicenter trials have looked into the safety and long-term efficacy of DEN. GEPARD study [78] included patients from six tertiary centers who underwent DEN and reported 81% clinical success and mortality rate of 7.5%. Gardner et al. reported a retrospective review from six US tertiary centers and noted a clinical success of 91% and mortality of 5.8% over a median follow-up of 17 months [79, 80]. DEN remains safe and effective approach in treatment of WOPN, however

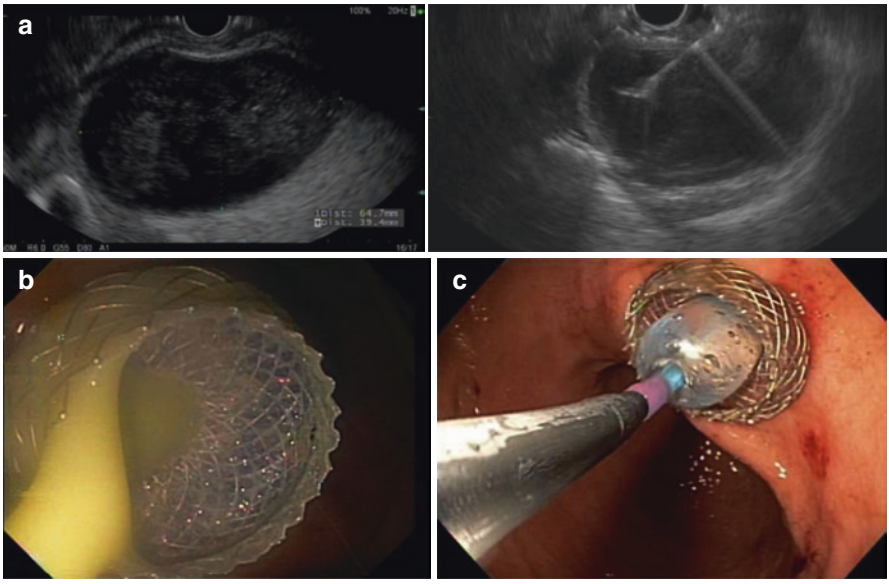

Fig. 7.9 (**a**) Walled-off pancreatic necrosis (WOPN) on endoscopic ultrasound view (arrow) and needle introduced inside the WOPN (arrow head) for the deployment of LAMS. (**b**) Endoscopic view of LAMS with pus draining out of the infected PFC. (**c**) Endoscopic view of balloon dilation of LAMS

requires expertise in the technique and is performed mostly in the tertiary centers with appropriate surgical support [81].

7.6 Complications

EUS-guided drainage of PFCs is deemed safe and reliable method of management. Fewer complications have been noted as compared to surgical and percutaneous procedures. Complications (Table 7.3) like perforation, bleeding (Fig. 7.11a), stent migration (Fig. 7.11b), and infection have been reported [66, 82]. Incidences of these complications have been reported to be <10% in most of the studies [83–85]. A recent meta-analysis showed LAMS to be superior and have higher efficacy and safety in the management of PFCs as compared to the plastic stents [86]. However, apart from the other listed complications, buried LAMS is a rare but serious adverse event [87, 88].

Hemorrhage is a common adverse event (AE) associated with the EUS-guided drainage of PFCs. Various factors can impact the occurrence of hemorrhage including type, size of PFC, stent type, operator experience, timing of procedure, and patient profile.

It can be intra-procedure caused by pseudoaneurysm, puncture of major or collateral blood vessels, traversing intracavitary blood vessel or post-procedure

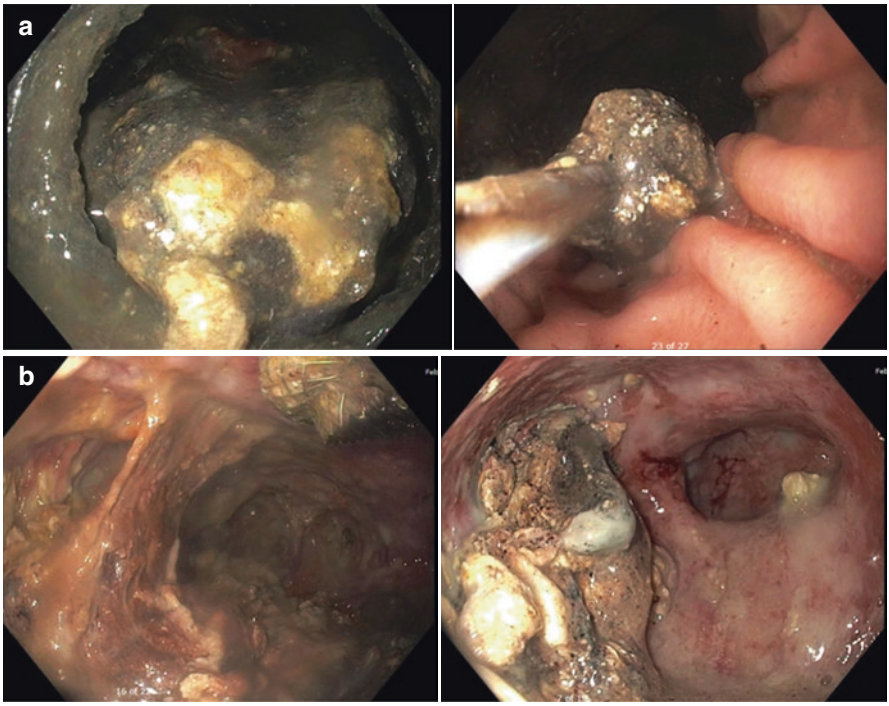

Fig. 7.10 (**a**) Endoscopic view of pancreatic necrosis through LAMS (left) and direct endoscopic necrosectomy being performed (right). (**b**) Endoscopic view of WOPN cavity with significant debris (left) and significant improvement after DEN (right)

Table 7.3 Common adverse events related with EUS-guided drainage

Adverse events	Patient related	Procedure related	Stent related
Factors	Coagulation disorders High-risk patient profile Aspiration Infection	Hemorrhage Perforation Pancreatic duct disruption Pseudoaneurysm Air embolism	Migration Occlusion Buried stent

associated with stent migration, buried stent, or coagulation defects [85]. LAMS when compared to DPPS is reported to have higher rate of procedure-related bleeding and pseudoaneurysm bleed in recent studies [89, 90]. These reported cases were managed successfully by transfusion, IR embolization of pseudoaneurysm, or with balloon tamponade under endoscopic guidance. On the contrary, a metanalysis reported higher technical success and low AEs for both pseudocysts and WOPN with bleed rate at 2.4% [66]. These adverse events need to be directly weighed against other risks including perforations and infections. Infections can occur with inadequate drainage of PFC or translocation if the bacteria to blood stream. Higher AEs are noted in PFCs requiring debridement and drainage of WOPN [13].

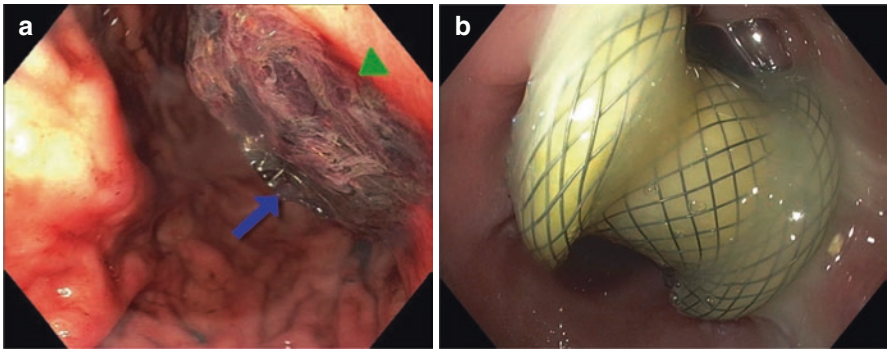

Fig. 7.11 (**a**) LAMS (arrow) with evidence of recent bleeding and adherent clots at the insertion site (arrow head). (**b**) Endoscopic view of LAMS migrated to the esophagus

7.7 Summary and Conclusion

Management of the PFCs is continuing to evolve with the advancements in technology, techniques, and availability of evidence. EUS-guided drainage of PFC is a safe and reliable modality when performed by experienced endoscopists, in a carefully selected patient by multidisciplinary team. It is safe to say that EUS-guided drainage is now considered sine qua non in the management of symptomatic PFCs. It is a safe and reliable approach with fewer complications as compared to surgical approach. However, innovation in the field of interventional EUS accessories is sorely needed to be able to continually enhance the success and safety of this modality.

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EUS-Guided Pancreatic Duct Drainage

8

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Advances in the field of interventional endoscopic ultrasound (EUS) have provided greater access to the pancreas and surrounding structures. Similar to the drainage of pancreatic fluid collections such as pseudocysts and walled-off pancreatic necrosis (WON) from the stomach or duodenum through endoscopic cystenterostomy or cystgastrostomy, the principle can be applied to access and drain the pancreatic duct. EUS-guided pancreatic duct drainage (EUS-PDD) is an alternative or second-line procedure which is used to drain the pancreatic duct when endoscopic retrograde cholangiopancreatography (ERCP), the primary modality for pancreatic duct drainage, has been unsuccessful or cannot be performed due to anatomic limitations [1].

As a complement or alternative to ERCP, EUS-PDD provides endoscopic therapy to patients who would otherwise be subjected to surgical or interventional radiologic (percutaneous) procedures for duct decompression. Traditionally, surgical intervention to provide pancreatic drainage includes lateral pancreaticojejunostomy (Puestow procedure) in patients with a dilated main pancreatic duct (MPD) or pancreaticoduodenectomy (Whipple procedure) versus distal pancreatectomy [2, 3]. Although surgery is effective in this setting with success rates of 65–85%, adverse event (AE) rates of up to 30% and mortality rates up to 2% have been reported [4]. Patients who underwent prior pancreaticojejunostomy creation with subsequent anastomotic narrowing or failure can have this anastomosis revised, although often at the cost of further loss of pancreatic parenchyma.

EUS-PDD can be performed within the same session of a failed ERCP depending on the expertise of the endoscopists [5]. However, majority of cases are

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performed by bringing the patient back to the endoscopy suite in the future. After transgastric or transduodenal EUS-guided pancreatography, the endoscopists can attempt drainage by means of the rendezvous method, wherein drainage can be achieved in antegrade, retrograde, or combined fashion with or without stent placement [1, 5]. Following successful drainage, patients typically require follow-up procedures for stent revision and/or removal [6].

EUS-PDD has demonstrated acceptable technical and clinical outcomes in a relatively small number of reported patients overall. A meta-analysis of 22 studies (714 patients) reported that EUS-PDD achieved a technical success rate of 84.8%, a successful PD drainage rate of 77.5%, and a clinical success rate of 89.2% [7]. The pooled rate of acute pancreatitis following EUS-PDD was 6.6% (95% CI 4.5–9.4), bleeding was 4.1% (95% CI 2.7–6.2), perforation and/or pneumoperitoneum was 3.1% (95% CI 1.9–5), pancreatic leak and/or pancreatic fluid collection was 2.3% (95% CI 1.4–4), and infection was 2.8% (95% CI 1.7–4.6) [7]. Given the nature of the procedure, there may be publication bias to these reported outcomes.

EUS-PDD remains a challenging procedure: (1) a dilated PD is very small relative to other traditional interventional EUS targets, including a pancreatic fluid collection, gallbladder, and even dilated bile duct; (2) during EUS-PDD, the stomach does not always provide a stable platform for an endoscope; (3) no dedicated PD stents designed for EUS-PDD are currently available, and (4) the pancreatic parenchyma must be traversed to reach the duct, increasing the technical difficult and risks of the procedure. Despite these challenges, EUS-PDD remains a feasible option for pancreatic duct drainage even in patients with altered anatomy [8].

8.1 Indications

EUS-PDD is employed when the typical clinical manifestations of pancreatic duct obstruction are clinically apparent and identified on imaging, and failed ERCP. EUS-PDD is not typically performed in the setting of resectable pancreatic cancer. The main indications for EUS-guided pancreatic duct drainage are stenosis of pancreaticojejunal or pancreaticogastric anastomosis after Whipple resection which induce recurrent acute pancreatitis. Additional indications include main pancreatic duct (MPD) stenosis due to chronic pancreatitis (CP), post-acute pancreatitis, or post-pancreatic trauma after failure of ERCP [9–13].

There are three main reasons for failure of pancreatic ERCP: difficulty in accessing the papilla (as in surgically altered anatomy or strictures), in cannulating the pancreatic duct, or in guidewire access to blocked duct segments (as in transected or disrupted ducts). On other occasions, the indication for EUS-PDD may arise during ERCP (e.g., failed guidewire passage across tortuous chronic pancreatitis strictures or impacted pancreatic duct stones). Indications for EUS-PDD include varying combinations of the following features.

8.1.1 Clinical Manifestations

1. Severe, persistent pancreatic-type abdominal pain consistent with pancreatic duct obstruction.
2. Acute relapsing pancreatitis felt to be secondary to pancreatic duct obstruction.
3. Refractory pancreatic fistula not amenable to standard ERCP.

8.1.2 Underlying Diagnoses

1. Chronic pancreatitis.
2. Pancreaticoenterostomy stricture.
3. Pancreas divisum.
4. Pancreatic trauma.
5. Pancreatic cancer.
6. Necrotizing pancreatitis.

8.1.3 Underlying Anatomy of the Pancreatic Duct

1. Strictures of the pancreas.
2. Stones within the pancreatic duct.
3. Disruption of the pancreatic duct.
4. A disconnected pancreatic duct.

8.2 Contraindications

8.2.1 Absolute

1. Uncontrolled and active perforation.
2. Unable to undergo sedation.
3. Unable to correct coagulopathy.

8.2.2 Relative

1. Non-dilated pancreatic duct (<3 mm).
2. Altered upper GI anatomy precluding EUS imaging of the pancreas (e.g., Roux-en-Y gastric bypass).
3. Inflammatory changes (e.g., pseudocyst) potentially interfering with optimal EUS access to the pancreatic duct.
4. Known resectable pancreatic malignancy.

8.3 Preparation

1. Patient evaluation and consent: Thorough clinical assessments, including cross-sectional imaging and magnetic retrograde cholangiopancreatography, are essential to establish the indication and to define procedural approach. Depending on anticipated likelihood of ERCP failure and on institutional policy, informed consent is obtained for both ERCP and EUS-PDD.
2. Periprocedural medications: Antiplatelet/anticoagulation agents and antibiotic prophylaxis should be managed per American Society for Gastrointestinal Endoscopy guidelines [14]. Though not established, administration of rectal nonsteroidal anti-inflammatory medications and intravenous hydration are reasonable to consider decreasing the risk of post-procedural pancreatitis.
3. Sedation: The level of sedation required for EUS-PDD is comparable to that of complexity level ERCP. Monitored anesthesia care, general endotracheal intubation, and nurse or endoscopist administered propofol can be provided depending on the availability of each institution.

8.4 Equipment and Devices

8.4.1 Equipment

1. Therapeutic channel linear-array echoendoscope (forward or forward-oblique viewing).
2. A duodenoscope (or colonoscope/enteroscope in cases of surgically altered upper GI anatomy).
3. High-quality fluoroscopy.
4. Image and ultrasound processors.
5. Carbon dioxide insufflation.

8.4.2 Devices

1. EUS fine-needle aspiration needles, most commonly 19G (21 or 22G may be considered for smaller ducts).
2. Injectate: Contrast material and saline solution.
3. Guidewires: Typically straight or angled-tip 0.025-inch or 0.035-inch high-performance hydrophilic long (450 cm) guidewires (for 19G needles). Thinner (0.018-inch or 0.021-inch) guidewires are required for 22G needles. Thicker (0.35-inch) and/or stiffer guidewires may be required for additional support during dilation or for better luminal coiling during the endoscope exchange phase of rendezvous. Guidewires of different tip configurations or hydrophilic coatings may have to be tried throughout the same procedure.
4. Low-profile steering catheters are commonly used for percutaneous interventional angiography or low-profile (3.5 French) taper-tipped ERCP cannulas.

5. Mechanical dilating catheters: Stepped axial dilators of 3–5-7 French diameter and balloon dilators of 4 to 6 mm diameter (less commonly, screw-type metal dilators; mechanical dilation is preferred over cautery dilation).
6. Cautery dilating catheters: Small caliber (6 French) cystotome is preferable to needle-knife, if locally available.
7. Plastic stents: Standard biliary (without side holes) or pancreatic (with side holes) 5 to 8.5 French, 7 to 20 cm long, straight or double pigtail stents are used (typically, straight 7 French).
8. Grasping devices (i.e., polypectomy snare, forceps).
9. Sphincterotomes: Either standard double or triple lumen (for antegrade guidewire steering) or dedicated (to facilitate parallel rendezvous cannulation).
10. Over-the-wire stone retrieval balloons: These allow occlusion antegrade pancreatography after fistula dilation and might be used to facilitate antegrade or retrograde pancreatic stone retrieval.

8.5 Techniques

There are currently two main approaches in achieving EUS-guided pancreatic drainage. These two approaches include EUS rendezvous pancreatic duct drainage and EUS anterograde/transluminal pancreatic duct drainage [15, 16]. The patient's specific and individual anatomy dictates the approach and guides technique and route of access selected.

8.5.1 Rendezvous Pancreatic Duct Drainage

An optimal access site is essential in achieving successful EUS rendezvous pancreatic duct drainage. Preferably, the optimal site is often the one that provides the shortest distance between the main pancreatic duct and a stable echoendoscope position without any interposed vasculature. Other factors to consider include the patient's anatomy. Nonetheless among patients undergoing EUS rendezvous PD, the optimal puncture site for easier guidewire manipulation is often at the neck of the pancreas compared to the body or tail of the pancreas.

After achieving a relative stable endoscope position, a puncture is made with a 19-gauge FNA needle. A 22-gauge FNA needle can be used to achieve access; however, this will require the use of a 0.018″ guidewire. Contrast is gently injected after needle puncture to obtain a pancreatogram to confirm needle access.

Following pancreatography, a 0.035 hydrophilic wire or 0.025-inch guidewire is carefully advanced under fluoroscopy and manipulated across the papilla into the duodenum or anastomosis site into the jejunum. The echoendoscope is then withdrawn leaving the guidewire in place and coiled into the small bowel as the echoendoscope is removed over the wire (Fig. 8.1).

A duodenoscope (in patients with normal foregut anatomy) or a pediatric colonoscope or an enteroscope (in patients with surgically altered anatomy) is inserted

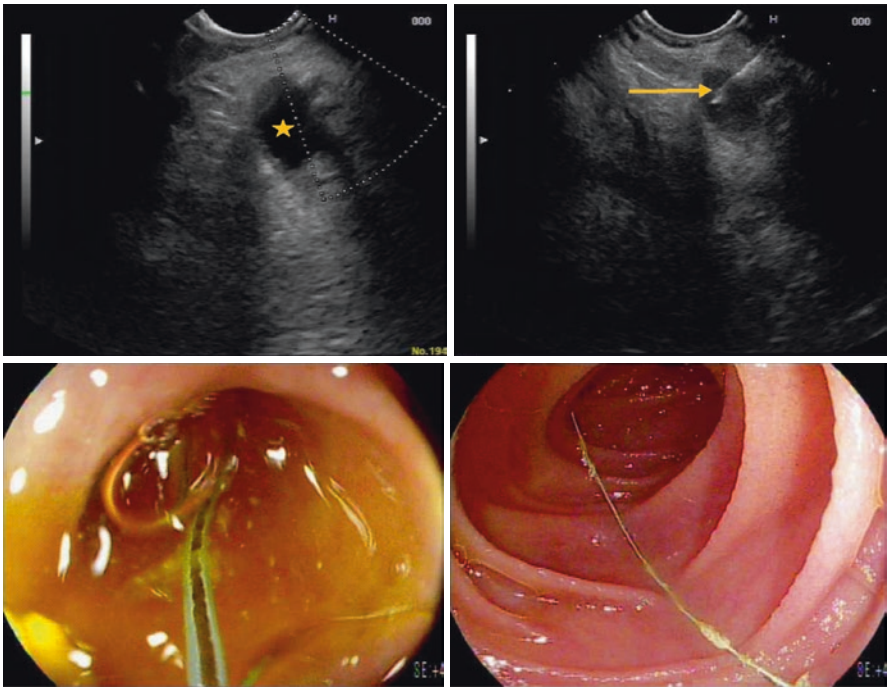

Fig. 8.1 Top images: Dilated pancreatic duct (star) and needle inserted for pancreatic duct drainage (arrow). Bottom images: Guidewire is carefully advanced antegrade across the papilla into the jejunum. Images courtesy Dr. Shai Friedland

towards the papilla or pancreaticoenterostomy anastomotic orifice. Cannulation is achieved by grasping the wire with a snare or biopsy forceps and gradually withdrawing the wire into the working channel for retrograde introduction of a sphincterotome or catheter over the wire. One must be mindful of not losing guidewire access during this exchange. Alternatively, a sphincterotome or cannula loaded with a second guidewire is inserted alongside the EUS-delivered guidewire to achieve cannulation (this practice is simpler to perform and is often used). Once cannulation is achieved, other therapeutic maneuvers including transpapillary or pancreaticoenterostomy anastomotic stenting can be achieved in the standard fashion.

8.5.2 Antegrade (Transluminal) Pancreatic Duct Drainage

Anterograde EUS-PDD is the preferred approach when the papilla or surgical anastomosis is endoscopically inaccessible [17]. Anterograde EUS-PDD is also indicated when anterograde transpapillary/transanastomotic guidewire passage cannot be achieved due to high-grade ductal/anastomotic obstruction or pancreatic ductal disruption [17].

The initial steps of EUS-guided transluminal approach involving pancreatic duct puncture and guidewire access into the main pancreatic duct are identical to the rendezvous approach. Once guidewire access is achieved, the major difference between the EUS rendezvous technique is the near universal need to dilate the transmural tract. The needle is exchanged over the guidewire for a dilator for fistula tract dilation. A passage or balloon dilator can be used.

Cautery of the needle tract followed by balloon dilation is used to create a fistulous tract to allow for stent placement. Using pure current electrocautery, the use of a 6.5 Fr Cystotome (Cook Medical) or a standard needle knife can also be used. Additional dilation can be performed with hydrostatic balloons up to 4 mm, particularly when stents are to be deployed. To avoid the risk of a pancreatic fluid leak, the tracts should be dilated to the smallest diameter to facilitate stent deployment.

8.6 Stent Placement

Stent placement can be subdivided into transluminal, transpapillary, or transanastomotic based on whether the stent traverses the site of ductal obstruction, the papilla, or the anastomosis. Crossing the papilla or anastomosis can be performed when feasible. Stents can be deployed in an antegrade (towards the head of the pancreas) or retrograde fashion (towards the tail of the pancreas).

When not feasible, transluminal stent placement is performed with one end of the stent in the pancreatic duct and the other end in the gastrointestinal lumen. In cases where the ampulla/anastomosis is crossed but not reachable endoscopically, transpapillary/anastomotic transluminal stent deployment is preferred.

There are several potential technical challenges to EUS-guided pancreatic duct access and drainage. There is risk of inadvertent parenchymal or vascular injection that may potentially cause tissue injury and/or reduce fluoroscopic visualization. Care should be taken to limit the volume and concentration of the contrast injected.

The guidewire often inadvertently passes into pancreatic duct side branches, which is prone to occur when there is a nearly perpendicular orientation of the echoendoscope to the desired duct. This problem may be overcome by altering the needle angle of entry and/or by selecting an alternate wire, for instance, a hydrophilic or angled wire. Guidewire passage across the papilla, anastomosis, or other site of obstruction may be difficult leading to wire buckling or inadvertent passage into undesired ducts or parenchyma. While gradual retraction and readvancement may suffice, at times the wire will not traverse the site of obstruction despite repeated efforts. Also consider insertion of a catheter or balloon into the duct near the site of obstruction. In this position, the catheter or balloon may serve to constrain and/or stiffen the guidewire and allow delivery of greater longitudinal force to facilitate wire passage through the site of obstruction.

Even with a guidewire in place, it may be difficult to pass a catheter or balloon across the gastric or duodenal wall, site of anastomosis, or another site of

obstruction. Catheter dilations are associated with an axial dilation force, which may lead to separation of the tissue planes with advancement. Balloon dilators, on the other hand, lead to radial dilation force, which may increase the risk of perforation, leaks, and bleeding. Prolonged pressure with either catheter may allow the device to suddenly pass. Initial dilatation with the needle sheath can aid passage as well. One may also consider selection of alternate devices that may traverse otherwise non-accessible strictures. Finally, one must always be mindful of the risk of wire shaving that occurs when retracting the wire into the needle at an acute angle.

8.7 Post-Procedure

Following sedation, patients should be monitored for 2–3 h for any anesthesia-related or immediate post-procedure adverse events. Depending on practice settings, EUS-PDD can be performed as an outpatient or inpatient procedure. Follow-up procedures are typically scheduled as outpatient procedures.

8.8 Adverse Events

1. Self-limiting abdominal pain.
2. Perforation.
3. Pancreatic duct leak with pseudocyst formation.
4. Abscess.
5. Acute pancreatitis.
6. Bleeding (acute or delayed).
7. Stent migration.
8. Stent obstruction.

8.9 Follow-Up

Duration of follow-up, interventions performed (stent removal, exchange, or upsizing), and their time intervals after index EUS-PDD are not standardized and are left to the individual provider given patient needs. Follow-up of rendezvous EUS-PDD mirrors the pattern of pancreatic ERCP, ranging from just one follow-up procedure for stent removal to several stent exchanges until resolution of the primary disease process is achieved. Transmural EUS-PDD can sometimes be converted to transpapillary (antegrade or retrograde) EUS-PDD at a follow-up procedure. Alternatively, a permanent fistula can be created by periodic exchange and/or upsizing of transmural stents at periodic month intervals over 12–24 months [18].

8.10 Conclusion

EUS-PDD is an alternative to ERCP which provides a less-invasive means for pancreatic duct drainage in patients who would otherwise be subjected to surgical or radiologic procedures. While EUS-PDD has demonstrable clinical and technical success for duct decompression, the complexities surround this technique allow only well-experienced endoscopists to perform the procedure. To date, only limited reports of EUS-PDD exist in the literature. EUS-PDD is mostly being performed at high-volume centers. However, as the field of EUS continues to grow, the application of EUS-PDD may become more available to patients who meet its criteria.

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9 Lumen-Apposing Metal Stents: Innovation in the Management of Pancreatic Fluid Collections

Juan E. Corral, Victor Ciofoaia, and Michael B. Wallace

9.1 Pancreatic Fluid Collections

Pancreatitis is broadly classified as edematous pancreatitis and necrotizing pancreatitis according to the Revised Atlanta classification (Table 9.1) [1]. Interstitial edematous pancreatitis can lead to acute peripancreatic fluid collections (APFC). Approximately one-third of APFC develop a mature outer wall and form a pancreatic pseudocyst over time (approximately 4 weeks). These lesions are filled with clear liquid with minimal or no debris. On the same spectrum, necrotizing pancreatitis follows a worse clinical course and evolves into acute necrotic collections (ANC). More than half of patients with ANC undergo a similar maturation process and develop walled-off necrosis (WON). Compared to pancreatic pseudocysts, WON is identified by solid necrotic debris on cross-sectional imaging [2].

These fluid collections are provoked by pancreatic enzyme digestion and are inflammatory in nature. If patients do not have clear history of acute pancreatitis, pancreatic cystic neoplasms should be considered among the differential diagnoses. The diagnostic workup and treatment of pancreatic cystic neoplasms is reviewed in Chap. 1 of this book. Inflammatory fluid collections are usually classified by cross-sectional abdominal imaging. Magnetic resonance imaging (MRI) has significant advantages over computed tomography (CT), improving debris identification (and thus the differentiation between pseudocysts and walled-off necrosis). MRI

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Table 9.1 Pancreatic fluid collections (Revised Atlanta Classification [1])

Imaging	Less than 4 weeks	More than 4 weeks
Without debris (complicates interstitial edematous pancreatitis)	Acute peripancreatic fluid collections (APFC)	Pancreatic pseudocysts
With debris (complicates necrotizing pancreatitis)	Acute necrotic collections (ANC)	Walled-off necrosis (WON)[a]

[a]Walled-off necrosis is further divided into sterile or infected walled-off necrosis (sWON and iWON, respectively)

following administration of secretin improves visualization of the main pancreatic duct and its side branches unveiling pancreatic duct disruption [3–5].

9.1.1 History and Paradigm Change

Over the last 20 years, drainage of pancreatic fluid collections has become a cornerstone in the treatment of severe pancreatitis. Drainage of fluid collections can be achieved with percutaneous, endoscopic, or surgical approaches. A recent randomized clinical trial showed similar survival rates between patients treated with endoscopic drainage and surgery. Endoscopic treatment however was superior in most of the secondary outcomes: lower rates of pancreatic fistulae, shorter hospital length of stay, and reduced costs [6]. This study recommended endoscopic ultrasound (EUS)-guided double-pigtail stent placement and a nasocystic catheter as a first step. In case of lack of significant improvement, endoscopic transluminal necrosectomy is the preferred treatment. Endoscopic drainage also has significant advantages over percutaneous drainage. In addition to allowing repeated interventions and improved quality of life (obviating the need to carry percutaneous tubes), it has fewer adverse events, in particular pancreatic-cutaneous fistulas [7]. Around the same time these trials were conducted, lumen-apposing stents (LAMS) were introduced into clinical practice. Early studies showed that LAMS were easier to deploy than plastic (double-pigtail) stents, shortening procedure time. Later on, they also prove to have higher technical and clinical success rates, particularly in patients with WON [8–10].

Early endoscopic techniques were only able to drain large pancreatic collections bulging transmurally or collections showing communication with the main pancreatic duct using a transpapillary approach. Transmural drainage was initially performed with regular endoscopy and needle aspiration followed by placement of plastic stents. Endoscopic ultrasound allowed treating smaller lesions, and those with less-intimate gastric contact, that did not bulge into the gastric or intestinal lumen. Interventional EUS accelerated with the development of self-expandable metal stents (SEMS), followed by the introduction of LAMS in 2011 and finally adding an electrocautery enhanced tip to facilitate deployment (“hot LAMS”) [11]. Over the last 10 years, different companies have designed LAMS variants with different lengths and diameters (see Devices).

9.2 Indications

Endoscopic drainage should be considered in all patients with symptomatic pancreatic fluid collections once the collection wall has matured, traditionally 4 weeks after acute pancreatitis episode. Symptoms include abdominal pain, dyspepsia, gastric/intestinal obstruction, biliary obstruction, and failure to thrive (Table 9.2). Patients developing cyst infection with fever, leukocytosis, acidosis, or other markers of systemic inflammatory response also benefit from endoscopic treatment. Patients with persistent organ failure despite maximum supportive therapy should be considered for prompt endoscopic drainage according to International guidelines [4]. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines published more recently also recommend treating patients with rapidly enlarging pseudocysts and any patient before attempting surgical interventions [12]. Lesions that meet drainage criteria can be approached with the following algorithm (Fig. 9.1). This chapter will focus on LAMS-guided drainage, recommendations on percutaneous and surgical (either video-assisted retroperitoneal debridement [VARD] or transgastric debridement) techniques can be found elsewhere [4, 14].

Traditionally endoscopic drainage of pancreatic lesions is avoided in early lesions (i.e., APFC and ANC). Performing drainage too soon can cause poor apposition between the cyst and the gastric (or duodenal) walls. Necrotic material can leak into the retroperitoneum and cause peritonitis. Occasionally, earlier (<4 weeks) drainage with a step-up strategy is performed in patients with necrotizing pancreatitis, developing infection and organ failure. Earlier interventions showed a relatively lower mortality without increase in adverse events, and similar improvement in organ failure if the indication for intervention was strong [15].

Table 9.2 Common indications for pancreatic fluid collection endoscopic drainage

Pancreatic pseudocyst and sterile walled-off necrosis (sWON)
Ongoing gastric, intestinal, or biliary obstruction due to mass effect
Persistent symptoms (e.g., vomiting, abdominal pain, "persistent unwellness")
Disconnected duct syndrome (i.e., full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting collection(s)
Rapidly enlarging lesion
Ongoing organ failure for several weeks after pancreatitis onset
Infected walled-off necrosis (iWON) (clinical suspicion or documented)
Clinical deterioration
Lack of improvement despite medical therapy
Special considerations
Wait for lesion to develop a mature wall (typically >4 weeks after onset of acute pancreatitis)
Pseudocysts should be >5 cm in their largest dimension
Do not perform routine aspiration to obtain bacterial cultures, and high rates of false-negative results have been reported

Based on ASGE [12] and IAP/APA management recommendations [4]

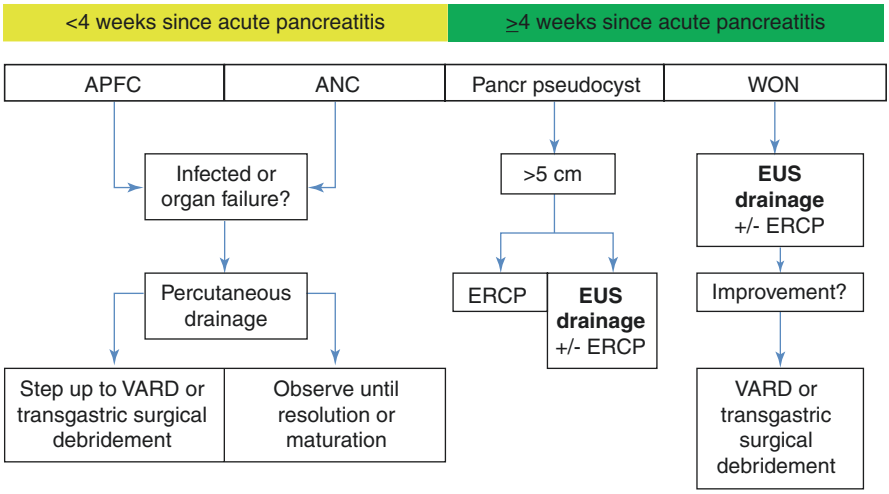

Fig. 9.1 Algorithm for the management of symptomatic pancreatic fluid collections (*ANC* acute necrotic collection, *APFC* acute peripancreatic fluid collection, *VARD* video-assisted retroperitoneal debridement, *WON* walled-off necrosis). Adapted from Elmuntzer BJ [13]

9.2.1 Technique

Endoscopic drainage of pancreatic fluid collections can be performed transpapillary with fluoroscopy and retrograde pancreatography or endosonographically. Different stents can be used (i.e., plastic stents, SEMS, and LAMS). The choice of technique largely depends on local expertise and anatomy. Collections abutting the stomach and duodenum are ideal for an EUS-guided approach. Simple pseudocysts with no or minimal necrotic material can be drained with 2–3 double-pigtail plastic stents, which is simple, low cost, and effective, and is covered elsewhere in this book. Patients with WON are best treated by LAMS to facilitate passive or active drainage of the necrotic material. Patients with large collections that extend into the pelvis or paracolic gutters or with multiple collections may require a combination of endoscopy-transmural and interventional radiology-percutaneous drainage. This section will focus on EUS-guided, LAMS technique. Preparation for the procedure involves reviewing patients' medications, laboratories, and imaging (Table 9.3).

Pancreatic pseudocyst drainage is usually achieved with a single intervention. If necrotic material is present within the fluid collection (WON), endoscopic necrosectomy may be needed. It is important to discuss with the patient the potential need for additional procedures from the index endoscopy.

The first step for drainage is adequate identification of puncture site. When fluid collections are large, a visible bulge is seen into the gastric or duodenal lumen. Some lesions, particularly those smaller or those located in the pancreatic tail, are only visualized with EUS [17]. Endoscopic ultrasound images identify a puncture site closest to collection and rule out intervening vascular structures (e.g., gastric varices) with Doppler (Figs. 9.2a and 9.3a).

Table 9.3 EUS transmural drainage checklist

Medications
Stop all anticoagulants and antiplatelet agents Stop antacids if possible (i.e., proton pump inhibitors and H2 blockers) Give prophylactic broad-spectrum antibiotics intravenously during the procedure (e.g., fluoroquinolone [16]), followed by oral antibiotics for 5–7 days
Laboratories and nutrition
Check type and screen, prothrombin time/international normalized ratio, and platelet count Verify 8 h fasting
Imaging
Cross-sectional imaging: Evaluate all vascular structures within or in close proximity with the collection (MRI preferred over CT) EUS imaging: Measure distance between the pancreatic collection and the intestinal lumen, ideally <1 cm. Doppler evaluation of vessels around fluid collection
Anesthesia
Provide general endotracheal anesthesia to reduce the risk of aspiration of cyst fluid that is drained into the upper GI tract. Few cases may benefit from paralytic agents during critical steps of puncture and deployment

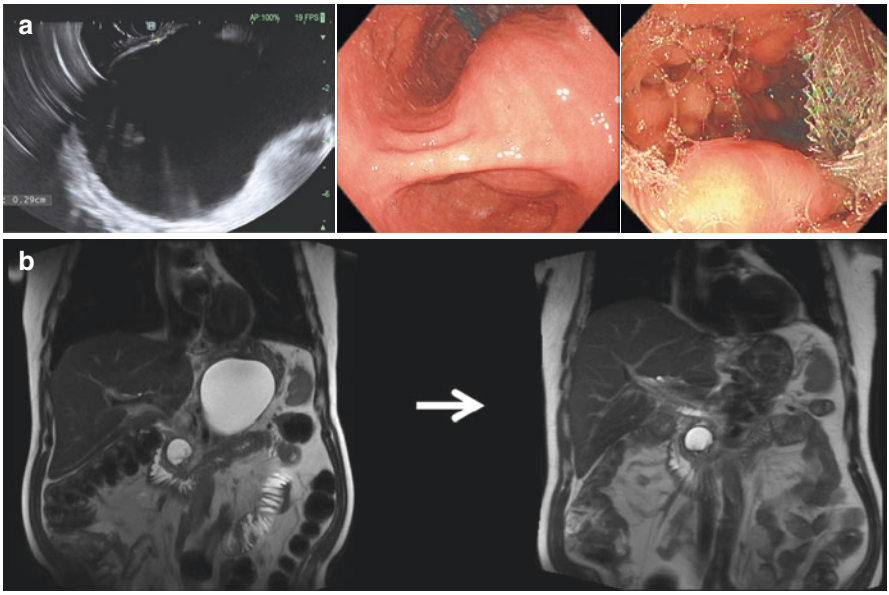

Fig. 9.2 LAMS drainage of pancreatic pseudocyst. (**a**) Endoscopic intervention. (**b**) Abdominal MRI before and after drainage

Hot-LAMS devices have a freehand thermal puncture system that facilitates penetration of the gastric or duodenal muscular layers. This is incorporated to the stent delivery system using the same sheath under EUS guidance [18–20]. Once the LAMS is deployed, liquid (clear in pseudocyst, turbid/purulent in WON) rapidly drains into gastric or duodenal lumen. Patients often experience rapid symptomatic

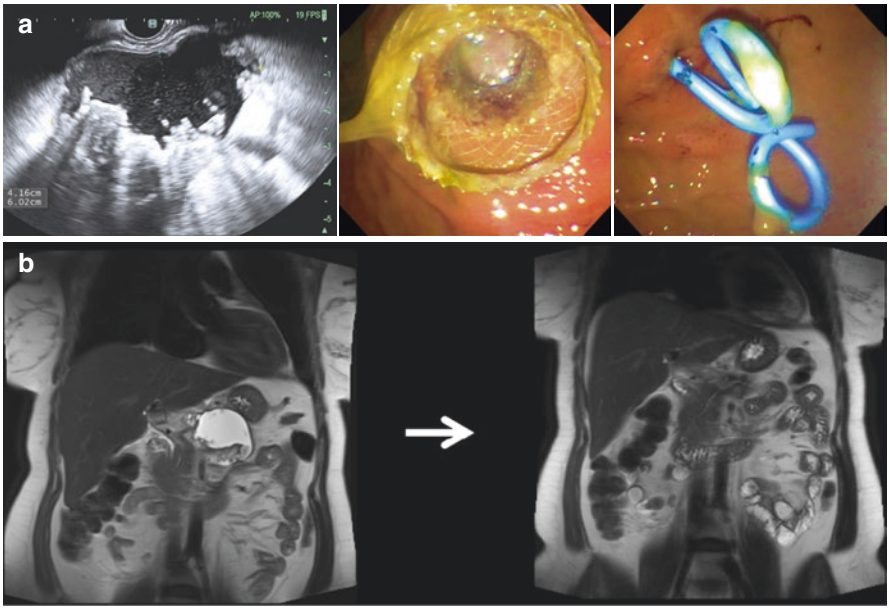

Fig. 9.3 LAMS drainage of sWON. (**a**) Endoscopic intervention. First LAMS is deployed, followed by two double-pigtail plastic stents placed 4 weeks later. (**b**) Abdominal MRI before and after drainage

relief after the procedure. In the past, nasocystic catheters were routinely placed to promote post-procedure lavage of necrotic material and debris. With the larger lumen and drainage provided by LAMS, this step is now considered optional. Puncture can also be performed with endoscopic knifes (e.g., precurved needle-knife sphincterotome or a cystotome (Cook Medical)). These techniques are reviewed in other review articles [21, 22].

We recommend against routine analysis of the fluid drained with cell count or cytology (only necrotic tissue and exudative material). Bacterial cultures should be sent only if there are concerns of infected pancreatic necrosis or if the lesion is more likely an abscess than walled-off necrosis. Patients only need to be admitted in the hospital if they develop worsening pain post-procedure, bleeding, or clinical deterioration. Endoscopists may hospitalize patients if they have limited healthcare access close to home in case symptoms ensue.

Patients should receive prophylactic intravenous antibiotics following ASGE guidelines and local susceptibility patterns [16]. This should be followed by five to 7 days of oral antibiotics (e.g., fluoroquinolone or extended spectrum penicillin). If pancreatic fluid was sent for culture, antibiotics should be adjusted accordingly. After the procedure, patients can drink clear liquids for the following 24 h and then advance to small, frequent low-fat meals (i.e., 30–50 g of fat per day). There are no specific activity restrictions, Table 9.4 [23].

Table 9.4 Post-drainage care and follow-up

Post procedure
Resume clear liquids same day for 24 h Advance diet to frequent low-fat meals as tolerated Avoid intense physical activity, but no definite activity restrictions
Do not attempt closure of cyst gastrostomy
Routine hospitalization is not necessary if patient is clinically stable and symptoms are mild
For pseudocysts and WON with small amount of debris, consider follow-up imaging in 4 weeks. If fluid collection has collapsed, remove stents If worsening symptoms, consider repeating drainage
For WON with significant debris (>40% of collection volume), consider repeating endoscopy with dilation and necrosectomy Leave 1–4 double-pigtail plastic stents for 3–5-year period
Oral antibiotics for 5–7 days Resume anticoagulation on a case-by-case basis

Usually, we recommend a follow-up CT scan, MRI, or EUS several weeks after drainage to assess complete resolution of the fluid cavity (Figs. 9.2b and 9.3b). If lesion was a pseudocyst, stents can be removed and patients monitored clinically. If there was necrotic material (>40% solid or turbid material), patients may need necrosectomy (see below) or leaving plastic stents in place despite radiographic resolution [24]. There is debate on how long plastic stents should remain in place, while some authors recommend indefinitely, we have seen plastic stents fistulize into the colon, hence advocate removing the stents after a 3–5-year period. Management of disrupted pancreatic duct and non-resolving fluid collections is complex and requires multidisciplinary approach with interventional radiology and surgery. General principles of disrupted pancreatic duct are reviewed elsewhere [25].

9.2.2 Available Devices

LAMS are fully covered, barbell-shaped, and self-expanding metal stents designed to secure the connection between the cyst and gastric (or duodenal) wall. At the time of writing, there are four LAMS options available: AXIOS and Hot AXIOS (Boston scientific Co., Marlborough, United States), NAGI and Spaxus (Taewoong Medical Co., Seoul, Korea), PSEUDOCYST stent (Micro-Tech, Ann Arbor, United States), and BCF stent (M.I.Tech Co., Seoul, Korea) (Fig. 9.4) [26]. The design and deployment systems are very similar. Different sizes are available with a luminal diameter of 6, 8, 10, 15, and 20 mm.

9.3 Repeated Interventions and Necrosectomy

Pancreatic pseudocysts usually improve after initial drainage. LAMS can be removed simply by pulling with a rat-toothed forceps using a regular front-view gastroscope. In WON, the amount of necrotic tissue helps decide if additional

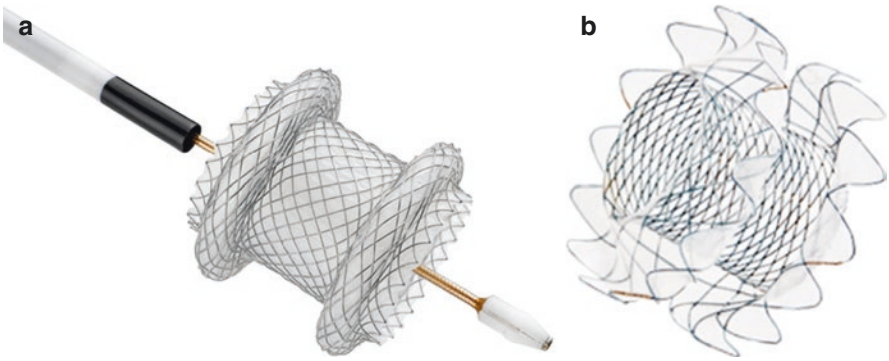

Fig. 9.4 (**a**) AXIOS stent and (**b**) NAGI stent

debridement is necessary. Fluid collections with >40% debris have lower changes to resolve spontaneously and benefit from necrosectomy [13].

Necrosectomy is removing debris and other necrotic material with snares, nets, lithotripsy baskets, foreign body graspers, and/or forceps through the previously placed LAMS. Depending on size of LAMS placed, endoscopist should dilate the tract with a balloon up to 18–20 mm, to allow transluminal entry of a front-view gastroscope and placement of plastic stents (between 1 and 4) [13]. Washing the necrotic area with hydrogen peroxide facilitates faster and more complete debridement. Small case series show this approach is safe when using a 1:5 to 1:20 dilution of 3% hydrogen peroxide. The solution can be flushed directly during endoscopy or via a nasocystic drain [27, 28].

If extensive adherent necrotic material remains after intracavitary endoscopic debridement, repeat debridement is typically performed every other day in hospitalized patients. If patients are stable and symptoms are mild, the procedures can be completed as outpatients and come back to the endoscopy room once a week until resolution (one case series reported a median of five procedures per patient) [29].

There is disagreement on whether necrosectomy is recommended in the index endoscopy. Most experts advocate waiting for the second endoscopy, but proceed if there is extensive necrosis or infection is identified [23].

Occasionally, the fluid collections are loculated into multiple compartments, and some portions are not drained by the first LAMS. Additional transmural stents combined with transpapillary drainage has been proven to be safe and effective. This technique is called multigated drainage [13].

9.4 Adverse Events

Successful resolution of collections is observed in 88–91% patients treated with LAMS based on recently published case series [30, 31]. Endoscopic drainage of pancreatic collections has significantly less adverse events than surgery, and a minimally invasive step-up approach (percutaneous or endoscopic drainage followed by

Table 9.5 Technical success, adverse events, and mortality after LAMS placement

Parameter	Reported frequency (%)	Reference
Technical success	84–98	[9, 34–36]
Clinical success	93	[9]
All adverse events Pancreatic pseudocyst WON	5–50 5–20 10–50	[9, 13, 37, 38]
Procedure adverse events	6–20	[30, 39]
Stent maldeployment	2	[8]
Acute bleeding	7	[35, 40, 41]
Perforation, pneumoperitoneum, and peritonitis	3–11	[31, 35, 39]
Delayed adverse events		
Recurrence	3–15	[34, 42]
Infection (with or without stent occlusion)	4–17	[8, 9, 35]
Delayed bleeding	0–25	[37, 39]
Stent migration (outward migration)	4–7	[9, 35, 38, 40]
Buried stent syndrome (inward migration)	0–17	[37, 38]
Biliary stricture	0–8	[37, 40]
Mortality	0–8	[34, 35] [40]

Estimates in this table include combined endoscopic interventions (i.e., LAMS with plastic stents)

video-assisted retroperitoneal debridement) is now recommended over primary open necrosectomy [32]. Endoscopic drainage also prevents incisional hernias, exocrine and endocrine insufficiency over long-term follow-up (86 ± 11 months in one study) [33]. Despite limited comparisons between different patient populations (pseudocysts vs. WON), interventions (LAMS-only vs. combined approaches), and varying definitions, adverse events develop in approximately 11% of patients, and procedure-related mortality is probably around 1% [30]. Table 9.5 summarizes the most important adverse events. Surgery is required in only 3–4% of cases [9, 40]. Overall, technical success is higher in patients with pancreatic pseudocysts, and adverse events are more common with WON [8, 43].

9.4.1 Procedure Adverse Events

Bleeding risk with LAMS is slightly higher compared to double-pigtail plastic stents. In a retrospective series of 313 patients, the rate of bleeding in the LAMS group was 7% (six patients) compared with 2% (two patients) in the plastic stent group and no patients in the fully covered SEMS group [41].

Acute bleeding usually presents when there is inadvertent laceration of intervening blood vessels. This can be avoided with Doppler visualization of vascular structures prior to puncture. Low volume bleeding from veins or small vessels can be treated with infiltration with a solution of 1:10,000 epinephrine, followed by endoscopic coagulation or hemostatic clipping. Large volume bleeding, frequently from a splenic pseudoaneurysm or gastric varices, usually requires IR embolization.

Endoscopic tamponade with a large caliber balloon should be attempted to permit fluid resuscitation and transport to the interventional radiology suite or operating room [13].

Stent malfunction or obstruction by solid necrotic material of food can lead to an infected or loculated fluid collection. This usually presents with worsening pain, fever, and leukocytosis. Such symptoms should prompt another endoscopy for stent cleaning and debridement. Infection is closely associated with the degree of pancreatic necrosis. Initially reported at high incidence (up to 50%) now is estimated to be much lower [44]. Post-procedure prophylactic antibiotics are administered routinely (Table 9.3).

Perforation is reported in 5% of cases, it usually develops when the fluid collection wall is poorly defined or there is more than 1 cm between the collection and intestinal lumen. In published case series, the majority of cases were managed successfully without surgery. Free peritoneal gas is frequently seen after drainage and not always represents ongoing abdominal contamination (CO_2 tracking). Stable patients with a reassuring abdominal examination can be treated with antibiotics and observation.

9.4.2 Delayed Adverse Events

Delayed bleeding is usually caused by LAMS slowly eroding into retroperitoneal vessels. LAMS are more likely to cause pseudoaneurysm bleeding than double-pigtail plastic stents [45]. Leaving LAMS in place for more than 4 weeks appears to be a significant predictor of bleeding, perhaps due to collapse of the cyst cavity and associated direct contact of the LAMS with vascular structures. As such, it is generally preferred to remove LAMS after 3–4 weeks and replace with plastic stents. If the fluid collection has not fully drained, coaxial placement of plastic stents through the LAMS is also reasonable with close surveillance [46].

Fluid collections can recur after drainage. Risk factors for fluid accumulation or protracted course are acute lesions, extensive necrotic tissue, thick walls (>1 cm), and lesions located in the tail of the pancreas [47, 48]. Reaccumulation of fluid is more frequent after combined drainage (i.e., transluminal and transpapillary). The transpapillary stent diverts pancreatic fluid drainage and prevents the maturation of the cyst-enterostomy fistula. Studies have not identified operator-related factors that predict stent occlusion [43].

Recurrence is also proportional to the extension of pancreatic duct disruption. It is seen in up to 50% of patients with disconnected pancreatic tail syndrome. Such patients have viable but disconnected segments of pancreas upstream [25]. Recurrence is also common with pancreatic duct strictures, residual biliary stones, or tumors. Placing additional pigtail stents through a LAMS can prevent recurrence.

Migration of the stent into the pancreatic pseudocyst is a relatively rare adverse event. A migrated stent can lead to secondary infection, abscess, perforation, or fistula formation. Stents can also erode into hollow organs causing fistulas (more frequently into the colon). The migrated stent needs to be retrieved with surgery, endoscopy, or percutaneous intervention.

The remaining delayed adverse events are secondary to damage caused by severe necrotizing pancreatitis rather than the procedure performed. Patients frequently develop pancreatic exocrine insufficiency and diabetes. Finally, 80% patients develop anatomic changes in the pancreatic ducts that resemble chronic pancreatitis. The clinical relevance of these changes is unknown [49]. A multicenter study suggests that the use of electrocautery (hot LAMS) may increase the risk of delayed adverse events [43].

9.4.3 Efficacy and Economic Considerations

Endoscopic drainage of symptomatic pancreatic collections (step-up approach) leads to shorter hospital stay compared to patients treated with surgery up-front. Compared to percutaneous treatment, endoscopy reduces the number of interventions, and number of follow-up abdominal imaging studies, and eliminates the risk of pancreatic-cutaneous fistula [6, 50].

Comparing the two main strategies, LAMS have higher success rates than plastic stents but the average cost per patient is significantly higher (U.S.$20,029 and U.S.$15,941 per patient treated with LAMS and plastic stents, respectively). The incremental cost-effectiveness justifies routine use of LAMS to treat WON, but plastic stents may be preferred for simple pancreatic pseudocysts [51, 52].

Finally, some endoscopists use the multigated LAMS technique. Considering the incremental cost of each stent, surgical treatment may become cost-effective in these patients [13].

9.5 The Future

Multiple questions in the management and follow-up care of patients with complicated pancreatitis remain unanswered. It is unclear if up-front necrosectomy is better and safer than step-up necrosectomy. The role of adjunctive irrigation and drainage strategies is based on expert opinion only and should be rigorously investigated. Prototypes of LAMS with an anti-reflux valve to facilitate one-way drainage of the collections, and multigated drainage have yet to be evaluated in a comparative prospective fashion [53]. Finally, the long-term benefits and adverse events of LAMS beyond 5 years need to be assessed.

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Endoscopic Pancreatic Necrosectomy

10

Carlo Fabbri, Cecilia Binda, and Chiara Coluccio

Acute pancreatitis is one of the most common gastrointestinal diseases; most of the cases are mild and self-limited. However, pancreatic fluid collections (PFC) are a frequent complication, and based on the updated Atlanta classification criteria, they are differentiated based on duration (less or greater than 4 weeks from onset of acute pancreatitis) and presence or absence of necrosis. Interstitial edematous pancreatitis can lead to acute PFC (<4 weeks) or pancreatic pseudocysts (>4 weeks). Necrotizing pancreatitis can lead to acute necrotic collections (<4 weeks) and walled-off peripancreatic necrosis (WOPN) (>4 weeks) [1]. Up to 10–20% of cases of acute pancreatitis can be associated with necrosis of the pancreas, peripancreatic tissue, or both. In this cluster of patients, the rate of mortality can reach 20%–30% if the infection occurs in the necrotic collection [2].

ESGE guidelines for the management of acute necrotizing pancreatitis recommend invasive interventions in case of: infected PFC, proven or clinically suspected, due to the highest risk of death in this subset; sterile pancreatic necrosis if symptomatic due to organ compression (persistent unwellness, abdominal pain, nausea, vomiting, nutritional failure, gastric outlet syndrome, intestinal or biliary obstruction, recurrent acute pancreatitis, fistulas, or persistent systemic inflammatory response syndrome); and abdominal compartment syndrome. Size alone, without symptoms, does not represent a criterion for drainage. The endoscopic ultrasonography (EUS)-guided approach, compared with surgical and percutaneous ones, is reported to be a valid option, taking into account the available expertise [3].

AGA guidelines, recently updated, agree on indications for drainage specifying that both percutaneous or transmural endoscopic drainage are appropriate first-line approaches although the endoscopic one may be preferred as it avoids the risk of creation of a pancreatocutaneous fistula [4].

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Endoscopic transmural drainage for pancreatic necrotic collections was first described in 1996, and over the years it has revolutionized, due to an exponential increase of EUS-guided interventional procedures and a growing variety of the available devices [5, 6].

Necrosis can involve any part of the pancreas, and it could be endoscopically reachable from both the stomach or duodenum, based on the location of the largest portion and the distance between the gastric or duodenal wall and the target cavity. Usually, collections near the pancreatic head are drained transduodenally, while those around the body or tail are drained transgastrically. Although the transgastric approach is most frequently used, both the approaches allow a direct endoscopic access to the collection, representing a gateway for direct endoscopic necrosectomy in order to remove the necrotic tissue that cannot be drained by the only presence of the stent [4].

EUS-guided drainage can be performed using plastic stents (PS), self-expandable metal stents (SEMS), or a dedicated device called lumen-apposing metal stents (LAMS). This stent is a fully covered, barbell-shaped, metal stent specifically designed for EUS-guided use (Fig. 10.1), which consists of two-side flanges with anti-migratory properties and a wide and short saddle that facilitates the creation of a stable fistula between the stomach or duodenal wall and the target cavity (variable according to the indication).

Although recent studies did not show different outcomes between EUS-guided drainage using PS or LAMS [7, 8]. LAMS seem to be preferred in the setting of WON in which they seem to provide satisfactory results and seem to be preferable [9–11].

Wider LAMS, indeed, allow the introduction of the endoscope through the stent to carry out interventional procedures in structures adjacent to the gastrointestinal tract, such as direct endoscopic necrosectomy (DEN) [12–14] and seems to be associated to lower number of DEN sessions [15].

Once a fistulous tract is created, the need for debridement is influenced by the amount of solid material within the WON. Debridement of necrotic tissue is a challenging procedure which represents a combination of different techniques [16]: suction of debris through the working channel, irrigation using antibiotics and/or hydrogen peroxide through the working channel or an endoscopically placed nasocystic tubes or percutaneously placed drains, and/or a direct endoscopic necrosectomy (DEN). DEN is performed directly introducing an endoscope into the cavity of the cyst and actively removing pieces of necrosis. DEN is usually performed with a therapeutic gastroscope, even if there is no evidence comparing different types of scopes (like double-channel, pediatric or standard) in this field [4]. Technically, a scope with a larger working channel makes easier the aspiration of fluids or small solid fragments and the entry of tools necessary for necrosectomy [17, 18].

The position of the site to puncture to gain the access to the collection is also taken into consideration for DEN; if it is too proximal (i.e., fundus or cardia) or distal (i.e., from the antrum), it may compromise the direct introduction of the scope into the cavity, making harder handling its manipulation.

Fig. 10.1 The Lumen-apposing Hot AXIOS stent (Boston Scientific Corporation, Natick, MA, USA)

Moreover, to date, no specifically dedicated devices were designed for DEN, but several endoscopic accessories have been used, such as grasping/rat-tooth/pelican forceps, polypectomy snares, retrieval nets, Dormia baskets, and stone extraction balloons (Fig. 10.2) [19–21].

The most commonly used are polypectomy snares and Dormia baskets, although no comparative trials are reported regarding the outcomes between the devices.

Recently, a novel automated mechanical endoscopic resection system called EndoRotor (Interscope, Inc., Whitinsville, Massachusetts, USA) has been described for DEN (Fig. 10.3). It is a catheter, driven by an electronically controlled console, which can be advanced through the working channel of the endoscope (of at least

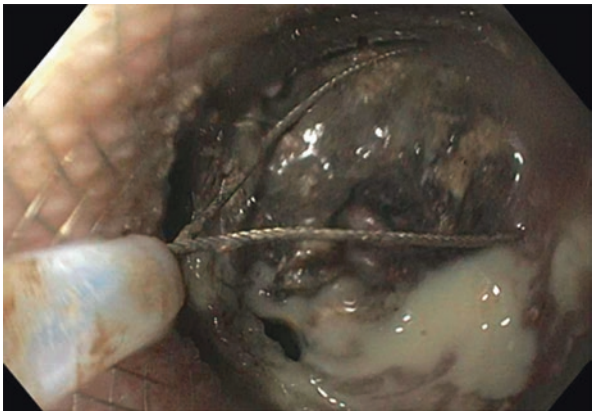

Fig. 10.2 Direct endoscopic necrosectomy using polypectomy snare

Fig. 10.3 EndoRotor (Interscope, Inc., Whitinsville, Massachusetts, USA)

3.2 mm in diameter) and has the function to suck, cut, and remove small solid fragments collected in the tissue collection trap. It is characterized by two rotating speeds (at either 1000 or 1700 revolutions per minute) and an increasing power of suction (from 40 L/min to 60 L/min), controlled by the endoscopist using two separate foot pedals. The cutter opening window of the device should be in direct contact to the necrotic tissue.

The catheter is flexible and able to tolerate endoscope torquing movements up to greater than 160°. Some reports have been described of successful DEN using EndoRotor system, even in patients who had previously been treated with conventional tools not reaching the resolution of the collection [22, 23].

In a case series published by van der Wiel et al. [24], a median number of two procedures was required to achieve complete removal of necrosis; using conventional tools, the mean number of interventions till recovery is reported to be about four per patient [25, 26].

Current literature indicates that this instrument is an encouraging option to achieve complete clearance of the pancreatic necrosis with lower number of DEN sessions; plus, the risk of bleeding using this new tool seems to be low, because necrosectomy is performed under constant endoscopic visualization, favoring successful treatment despite the presence of vessels inside the collection [22].

Regardless the type of devices used, it is still debating whether DEN should be done up-front, namely just following stent placement, or delayed to another session, and whether to perform it scheduled or "on-demand."

DEN, indeed, has been considered as part of the step-up approach of EUS-guided drainage of pancreatic fluid. Standing to this approach, DEN, which is considered a high-risk procedure, should be taken into consideration after failure of transmural drainage and irrigation through a nasocystic tube [27, 28].

However, a precocious session of DEN, during the initial endoscopic access into the necrotic cavity in a single-step intervention, has also been described demonstrating reduced rates of complications and mortality rate [18, 19, 29].

Although no strong indications are provided, Fig. 10.4 represents the flowchart proposed by the latest American practice guidelines (Fig. 10.4) [4].

Major complications related to DEN are represented by intracavitary bleeding (the most common and fearsome), air embolism, and perforation, with an overall complication rate that could rank 36% [4, 30]. Although these complications are often self-limited and can be treated conservatively, in some cases they may require endoscopic re-intervention, mainly mechanical hemostasis, or radiological or surgical interventions, becoming potentially life-threating [30–32].

Another important issue is about timing for DEN, which has been changing in the last years. Although 4 weeks have been used as threshold for the development of a mature wall of the collections and therefore as perfect timing beyond which transmural drainage and DEN should be performed, data are emerging on precocious treatments. When there a strong indication is present, like infection and organ failure, an early (<4 weeks) endoscopic drainage is effective and does not carry an increased risk of complications, although a slightly increased need for surgery is reported [33].

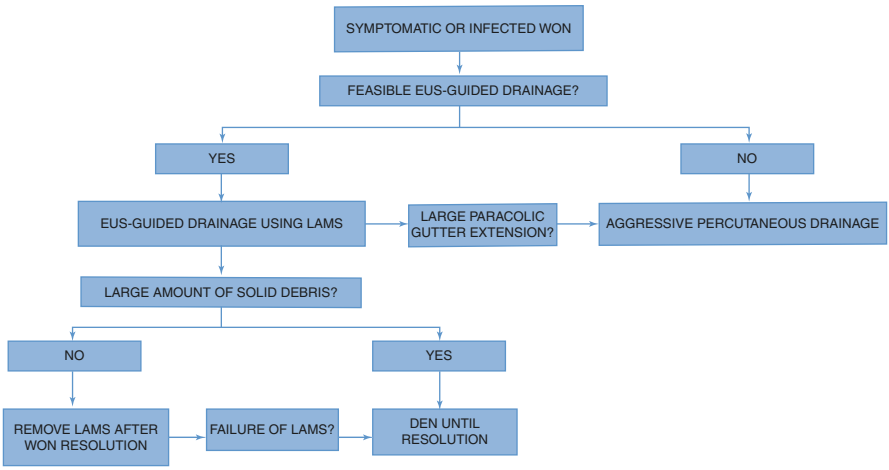

Fig. 10.4 Flowchart adapted from AGA guidelines. *WON* walled-off necrosis, *EUS* endoscopic ultrasound, *LAMS* lumen-apposing metal stent, *DEN* direct endoscopic necrosectomy

A topic which is emerging for the management of pancreatic necrosis is proton pump inhibitor (PPI) use in these setting of patients. In 2016, Thompson et al. [29] demonstrated that, among 60 patients undergone to necrosectomy, discontinuing PPI therapy may lead to autodigestion of the necrotic tissue by physiologic gastric acid production and further address potential infectious complications. A more recent multicenter retrospective study on 272 patients undergone to EUS-guided drainage for WON showed a statistically significant number of DEN needed for the resolution of the necrosis for those patients in which PPI were discontinued (3.2 number of DEN vs. 4.6) [34]. The most recent published American guidelines on management of pancreatic necrosis [4] mention this topic assessing that, despite experienced endoscopists have recommended avoidance of proton pump inhibitor after transmural drainage, data are lacking to strongly recommend this practice.

Not least, "hard-to-treat" conditions are represented by those necrotic collections which are far from the gastrointestinal walls and, therefore, not amenable to transluminal drainage, and by necrosis extended to the pelvic paracolic gutter. In all these cases, a percutaneous drainage alone or as dual approach is recommended [3, 4]. However, percutaneous catheter, even when larger ones are used, could be insufficient for the drainage of the solid component and do not allow to perform direct necrosectomy, with reduced possibility of resolution of the necrosis. On the other hand, surgical necrosectomy, even with a minimally invasive approach, is burdened by high mortality and complication rates, so that should be reserved only for patients with persistent organ disfunction and failure to thrive [4, 35, 36].

For all these reasons, even considering that complex necrotic collections are potentially life-threatening and lacking of standard treatment, a percutaneous endoscopic necrosectomy (PEN) through esophageal SEMS has been proposed, showing promising results [37]. This technique has been previously reserved to those patients in which an endoscopic drainage was contraindicated or technically impossible, although in further case series has been used also for patients with a previous endoscopic transmural drainage [37–44].

Technically, a 0.035-inch guidewire is advanced through a previously placed transcutaneous catheter and coiled within the target cavity under fluoroscopic guidance; the catheter is then removed leaving the wire in place; the tract usually undergone to pneumatic dilation over the wire under fluoroscopic guidance. Then, a fully covered SEMS is inserted into the fistulous tract and again a dilation with balloon is performed under fluoroscopy in order to achieve an adequate diameter for the introduction of an endoscope (Fig. 10.5). Usually, a gastroscope is preferred and introduced into the collection through the esophageal stent in order to perform necrosectomy. The metal stent is sutured to the skin and subsequent percutaneous debridement sessions can be done until complete resolution. In addition, a catheter can be placed through the SEMS between each session of PEN for continuous lavages or local instillation of antibiotic. After the removal of SEMS, the fistulous tract can be kept healing by secondary intention [42].

In a recently published case series [42], the technical success and clinical success rate were 100% and 89%, respectively, without need for additional endoscopic

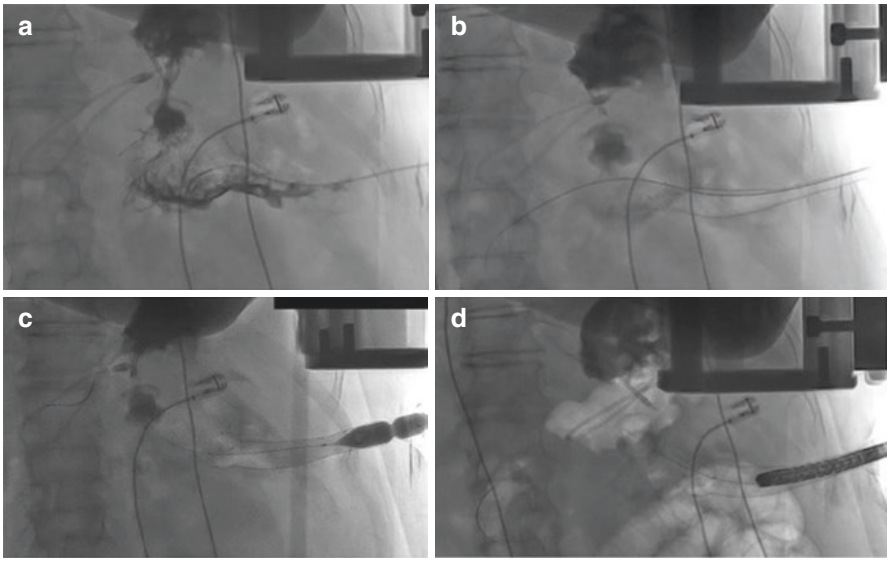

Fig. 10.5 (**a**) Fluoroscopic view of the necrotic collection by the catheter previously placed. (**b**) Placement of the fully covered esophageal SEMS under fluoroscopic guidance. (**c**, **d**) After placement of SEMS, the CRE balloon was used to dilate esophageal stent, allowing the passage of a gastroscope

interventions. This suggests that PEN, in some special conditions, is an effective alternative method to bear in mind.

However, only case report and case series with few number of patients are reported so that these technique is not, to date, included in the international guidelines.

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Role of Endoscopic Ultrasound in Pancreatic Cancer Screening

11

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11.1 Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in Western societies [1–3]. Ductal adenocarcinoma and its variant account for over 90% of all pancreatic malignancies. Some patients may be symptomatic with weight loss, jaundice, malabsorption, pain, dyspepsia, and nausea, but many patients are asymptomatic; no early warning signs of pancreatic cancer have been recognized [3]. As pancreatic cancer often develops with few symptoms, only 10–20% of patients are diagnosed at a stage amenable to resection, the only possible cure [4]. The overall 5-year survival of pancreatic cancer is below 5% combining all stages, but it is about 2% in patients with distant metastases [4].

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One reason for the poor survival seen in patients with pancreatic cancer is the difficulty to diagnose it early [5]. Pancreatic neoplasia, if detected early, is potentially curable. Therefore, it is important to screen patients at risk. However, most clinical risk factors for pancreatic cancer are nonspecific, including age, smoking habit, diabetes mellitus, obesity, and chronic pancreatitis [4]. For this reason, and because the incidence of pancreatic cancer in the general population is low, population-based screening is not recommended. Nonetheless, some specific risk factors for pancreatic cancer have been identified. This chapter discusses the role of EUS in pancreatic cancer screening in patients with risk factors.

11.2 Risk Factors for Pancreatic Cancer

The main risk factors for pancreatic cancer are a family history of the disease, inherited cancer syndrome (mutation carriers), pancreatitis, new onset of type 2 diabetes in elderly persons, and precancerous lesions of the pancreas [1, 4, 6–9].

A hereditary component has been found in 1–10% of patients with pancreatic cancer [10]. Family history is the main feature used to stratify PC risk, and screening is recommended [2, 4] for individuals with:

- Three or more blood relatives with PC, with at least one affected first-degree relative (FDR)
- At least two affected FDRs
- Two blood relatives with PC, with at least one FDR

Germline mutations in the *BRCA2, PALB2, p16, STK 11, ATM,* and *PRSS1* genes and in hereditary colon cancer genes are associated with significantly increased risk of PC [2]. Characteristics of persons to be screened [2, 4] are:

- Patients with Peutz-Jeghers syndrome, regardless of a family history of PC
- CDKN2A/p16 carriers (familial atypical multiple mole melanoma) with one affected FDR
- *BRCA2* mutation carriers with one affected FDR (or two affected non-FDR family members)
- *PAlB2* mutation carriers with one affected FDR
- Mismatch repair gene mutation carriers (Lynch syndrome) with one affected FDR

Individuals with hereditary pancreatitis have a high life-time risk for pancreatic cancer [2]. Genes associated with susceptibility to pancreatitis are *PRSS1*, *CPA1,* and *CRTC* [1], but the risk is also associated with the duration of recurrent pancreatitis and chronic inflammation [2].

The risk of pancreatic ductal adenocarcinoma in people with long-standing type 2 diabetes is 1- to 1.5-fold higher than in the general population, and it is 5.4-fold higher in people who have had type 2 diabetes for less than 1 year [9]. The onset of

diabetes is considered an early warning sign of pancreatic ductal adenocarcinoma, and individuals with diabetes form the highest risk group for sporadic pancreatic ductal adenocarcinoma [9].

Three noninvasive precursor lesions of PC have been described:

- Intraductal papillary mucinous neoplasm (IPMN)
- Mucinous cystic neoplasm (MCN)
- Pancreatic intraepithelial neoplasia (PanIN)

Most mucinous pancreatic cysts are IPMN, which accounts for less than 10% of all pancreatic cancers.

If they are associated with high-grade dysplasia, they are at more risk of invasive PC. The detection and early treatment of high-grade dysplasia IPMN is a success of screening/surveillance programs [4].

They can be categorized based on the location and extent involvement within the pancreas as main duct intraductal papillary mucinous neoplasm (MD-IPMN) with an incidence that varies from 57 to 92%, branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) with an incidence from 6 to 46% and mixed types (MT-IPMN) [4, 6].

Recently, International Cancer of the Pancreas Screening Consortium has proposed successful screening as the detection and treatment of T1N0M0 margin-negative pancreatic cancer and high-grade dysplastic precursor lesions, including PanIN-3, IPMN with high-grade dysplasia, and MCN with high-grade dysplasia [2, 5].

11.3 Pancreatic Screening Tools

It is essential to know the risk of pancreatic neoplasia for each patient to stratify high-risk group, so a detailed medical history is necessary.

There are no clear guidelines concerning the proper age to start screening. Screening in many institutions is started at the mean age or the youngest age at onset of PC in the family. Other authors recommend screening at the age of 40–45 years or 10–15 years younger than the youngest relative with PC. The American College of Gastroenterology advocates that surveillance should be with EUS and/or MRI of the pancreas annually starting at age 50 years, or 10 years younger than the earliest age of PC in the family [4, 5, 11]. In patients with PJS, screening is recommended at age 30–35, and in *PRSS1* mutation carriers with hereditary pancreatitis, it should begin at age 40 [4, 11–13]. Many institutions prefer yearly screening if the latest EUS and/or CT is normal. Subsequent screening is done every 3–6 months or 2–12 months if an abnormal finding is observed. The interval screening adopted for non-suspicious cysts is 6–12 months, 3 months for a newly detected solid lesion if surgery is not imminent and 3 months for an indeterminate main pancreatic duct stricture [11].

11.4 Diagnostic Imaging Modalities for Pancreatic Cancer Screening

Considering the imaging studies, there is no consensus regarding the best method for pancreatic cancer screening. The principal imaging modalities to detect pancreatic tumors [4] are endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), multidetector computed tomography (MDCT), positron emission tomography (PET), probe-based confocal laser endomicroscopy (pCLE), and endoscopic cholangiopancreatography (ERCP).

EUS and MRI are considered the best choice for screening high-risk individuals, avoiding radiation exposure.

EUS provides high-resolution images of the pancreas, accurately detects IPMNs, and visualizes characteristics of increased risk of malignancy (such as thick internal septations, mural nodularity, solid masses, main pancreatic duct (MPD) dilatation, filling defects in the MPD and vascular invasion) [2, 4, 6, 11, 12].

pCLE is an advanced endoscopic technique that can provide a dynamic real-time imaging of the mucosa at subcellular level allowing the identification of suspicious architectural changes [14]. Probe-based confocal laser endomicroscopy (pCLE) has recently appeared as a technological improvement to EUS with a particular role in cystic lesions evaluation [4].

11.5 Screening and EUS

The only endoscopic method clinically used for pancreatic cancer screening is EUS [15].

11.5.1 EUS in Patients with a Family History of Pancreatic Cancer

In individuals with a family history of pancreatic cancer, it is very important to identify preinvasive lesions with high-grade neoplastic changes [11]. Imaging in high-risk families can detect precancerous changes associated with increased risk for invasive pancreatic cancer [11]. Early detection of precancerous lesions permits the treatment of individuals with curative surgery [7]. With high agreement among consortium experts, EUS and MRI are considered the most accurate image tools to screen individuals with family history of pancreatic cancer [16].

Bartsch et al. in their study [8] showed that 53% of individuals with family history of pancreatic cancer revealed pancreatic lesions on imaging. These lesions were primarily cystic and found in persons above 45 years [8]. The study suggests to add EUS to MRI at baseline, every 3 years or when a suspicious lesion is found during follow-up [8]. The importance of EUS in screening of familiarly high-risk population is underlined also by Verna et al. [17] where EUS findings, in family history of pancreatic cancer individuals, highlight that 29% of these patients

present parenchymal changes typical of chronic pancreatitis and 6% had a mass lesions confirmed later with FNA to be adenocarcinomas. Their series confirms that malignant and premalignant lesions can be discovered during EUS screening, and disease progression could be prevented with pancreatic surgery. Moreover, Canto et al. [18] reported that in high-risk individuals with family history of pancreatic cancer, EUS abnormalities suggestive of chronic pancreatitis were very common [18]. Finally, a recent report of the American Society of Clinical Oncology recommended high-risk pancreatic cancer individual screening and follow-up based on MRI and EUS [19].

11.5.2 EUS in Pancreatic Cancer Associated with Inherited Cancer Syndrome (Mutation Carriers)

Life-time cumulative risk of pancreatic cancer in individuals with PJS is from 11 to 36% with a mean age at pancreatic cancer diagnosis of 41 years [2, 12, 20]. As for familiar pancreatic cancer risk, early detection of precancerous lesions is very important for the prognosis. EUS is an important tool to find precancerous lesions or pancreatic abnormalities in these patients.

Canto et al. demonstrated that in individuals with a strong family history of pancreatic cancer or with PJS, EUS-based screening can be essential to find pancreatic neoplastic lesions or pancreatic neoplasms [21].

Moreover, DaVee et al. in their study reported that in individuals at risk for pancreatic cancer and with inherited cancer syndrome, EUS-based screening permitted a better detection of abnormal pancreatic findings like cysts, hyperechoic strands and foci, and mild pancreatic duct dilatation with respect to MRI [22].

11.5.3 EUS in IPMN

MRCP is the initial imaging technique to diagnose and evaluate IPMN but EUS improves the accuracy of the assessment of pancreatic parenchyma and allows the possibility to perform biopsy that can be useful to classify preoperatively IPMN according to its histopathological subtypes [4]. BD-IPMN and MD-IPMN are visible on cross-sectional scans and with EUS [10].

Invasive carcinoma incidence in MCN varies and preoperative diagnosis depends on a combination of parameters. EUS has a major role in the diagnosis of these lesions permitting a better evaluation of the wall as it may show separation or nodule within the cyst and can permit a biopsy of the wall and an aspiration of the cyst content [4]. PanINs are asymptomatic and considered precursor lesions in the stepwise progression from intraepithelial to invasive pancreatic neoplasia. They are microscopic lesions which might cause some tiny or abdominal finding in imaging [5] not detectable by cross-sectional imaging. Since multifocal PanINs can produce multifocal lobulocentric atrophy giving rise to the pancreas an appearance similar to

that of chronic pancreatitis, it can be possibly detected by EUS [4]. High-risk individuals of PanIN can present EUS findings like heterogeneous parenchyma, hypoechoic nodule, hyperechoic main duct wall, and discrete masses [12].

There are some proposed high-risk stigmata or worrisome features to help for picking up true meaningful or suspected malignant pancreatic cystic lesions or IPMN to avoid unnecessary operation or overtreatment [5]. Patients with worrisome features, specifically cyst >3 cm, thickened/enhanced walls, main duct 5–9 mm, non-enhancing mural nodule, or abrupt change in caliber of pancreatic duct or distal pancreatic atrophy, were elicited to EUS-FNA. Patients without worrisome features were managed based on the size of the cyst:

- 1 cm, CT/MRI surveillance in 2–3 years
- 1–2 cm, placed into a yearly surveillance program
- >2 cm, managed with US-FNA
- >3 cm, surgery recommended if the patient is well fitted

If there are nodular lesions, duct dilatation, or jaundice of EUS, surgical resection is recommended [4].

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Endoscopic Ultrasound in Pancreatic Cancer Staging

12

Nan Ge and Siyu Sun

Pancreatic cancer (PC), which has a 5-year survival rate of 6.0%, is the seventh leading cause of cancer-related deaths worldwide. However, only 10–15% of patients have an early diagnosis and a chance for potential curative resection [1]. Optimal therapy is established based on accurate cancer staging. Therefore, PC staging is mandatory and important in clinical practice.

Endoscopic ultrasound (EUS) is currently the most sensitive imaging test available for examining the pancreas and associated structures. Small (<2 cm) pancreatic malignancies can be detected with accuracy rates of more than 90% using EUS. EUS-guided fine needle aspiration (EUS-FNA) was established in the early 1990s and is now considered one of the standard procedures for diagnosing PC [2]. The applications of EUS and EUS-FNA are constantly widening, from only diagnosis to including staging as well [3–7].

EUS staging of PC is mostly based on the tumor–node–metastasis (TNM) system provided by the American Joint Committee on Cancer (AJCC). According to the literature, the accuracies of T staging with EUS range from 62 to 94%, and those of N staging with EUS range from 50 to 86% [8, 9]. This range may be due to the use of different staging editions, the continued development of EUS techniques, or the examiners' biases. In 2001, based on the fifth edition of the AJCC staging, one study reported that the overall accuracy of EUS for T and N staging was 69% and 54%, respectively [10]. The overall proportion of tumors that were deemed resectable after evaluation using EUS and were actually found to be resectable during surgical exploration was 46%. The authors of that study concluded that in a tertiary referral patient population, EUS is not as accurate as previously reported in the T and N staging of PC. EUS is also not predictive of resectability in stage T3 or T4

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Table 12.1 AJCC staging system for pancreatic adenocarcinoma (8th edition)

Primary tumor (T)		Regional lymph nodes (N)		Distance metastases (M)	
TX	Primary tumor cannot be evaluated	**NX**	Regional lymph node metastasis cannot be evaluated	**M0**	No distant metastases
T0	No primary tumor	**N0**	No regional lymph node metastasis	**M1**	Distant metastases
Tis	Carcinoma in situ	**N1**	1–3 positive regional lymph nodes metastasis		
T1	Maximum tumor diameter ≤2 cm T1a: ≤0.5 cm T1b: >0.5, <1.0 cm T1c: ≥1, ≤2 cm	**N2**	≥4 regional lymph nodes metastasis		
T2	Maximum tumor diameter >2 cm, ≤4				
T3	Maximum tumor diameter >4 cm				
T4	Tumor involves the celiac axis, the superior mesenteric artery, or common hepatic artery				

PC. In 2014, a meta-analysis reported that the sensitivity of EUS for T1–T2 stages is 76% but is significantly higher in patients with T3–T4 stages, reaching 90% [11].

The recently published eighth edition of AJCC staging for PC has undergone major changes in the T and M staging compared with the previous editions [12, 13]. Extra-pancreatic extension is no longer part of the T staging, and size-based definition has been introduced to define T1 to T3. N1 has been subdivided into N1 and N2, based on the number of positive lymph nodes. These updates are based on novel evidences and reflect a deeper understanding of PC (Table 12.1). The study has proved that the eighth edition provides more even distribution with more powerful discrimination compared to the seventh edition [14]. Till date, studies focusing on PC staging with EUS based on the eighth edition of AJCC staging are limited. Therefore, in our study, we aimed to assess the EUS staging ability by reviewing the individual EUS diagnostic capability for tumor size measurement, vascular invasion detection, and malignant lymph node detection. Furthermore, the contribution to the pathological diagnosis on using EUS-FNA in the tumor staging was discussed.

12.1 EUS for Tumor Size Measurement

EUS is superior in determining the locoregional staging of PC compared with other cross-section imaging modalities. Most PCs on EUS image appear as hypoechoic heterogenous lesions with irregular margins. According to the eighth edition of JACC staging, T1–T3 staging for PC is based on the accurate size measurement. In a study published in 2011, the authors compared the tumor size measured with computed tomography (CT) and EUS before surgery with the actual resected specimens obtained after surgery. It was seen that 84% of patients had a primary tumor 7 mm

larger on pathology than CT. In comparison, EUS was found to be more accurate, with pathologic tumor size being a median of only 5 mm larger compared with the size detected using EUS [15]. In 2014, a meta-analysis by Li et al. also reported that the accuracy of EUS in the nodal staging is lower, with a sensitivity of 62% and a specificity of 74% [11].

The accuracy of EUS measurement in determining PC size could also be hampered by some other factors, like chronic pancreatitis (CP). The incidence of PC in patients with CP is as high as 5%. It is a commonly encountered diagnostic challenge in patients with CP on long-term follow-up. EUS sensitivity is decreased in calcific CP with shadowing stones.

Elastography and contrast-enhanced (CE)-EUS may also contribute in outlining local or regional tumors. In most patients, pancreatic malignancy appears on EUS as a typically hypoechoic mass with indistinct margins, which is rarely missed. However, sometimes a pancreatic mass will appear isoechoic on EUS imaging, which could still be successfully identified by a sign of "cut-off" in the pancreatic duct and/or common bile duct [16]. In this situation, tissue elastography and contrast-enhanced ultrasound may be helpful in determining the outlines of the tumor and may hold promise in such rare cases [17]. The elasticity or microvascular pattern could be different between inflammatory and cancerous components. These ancillary techniques can be used to improve characterization of the lesion along with EUS. Bunganic et al. reported that the accuracy of EUS and CE-EUS for diagnosis PC is 78.6% and 84%, respectively; moreover, CE-EUS is a noninvasive method that allows more accurate identification of PC than EUS. Angiogenesis revealed using CE-EUS is an important factor that influences the prognostic of solid tumors. Therefore, Saftoiu et al. performed a study to determine the changes in tumor vascularity depicted with CE-EUS as a predictor of prognosis and treatment efficacy in patients with unresectable PC [18].

12.2 EUS Detection for Vascular Invasion

Peripancreatic vasculature involvement with tumor is identified as the T4 stage. Additionally, the assessment of PC resectability is based mainly on the extent of the tumor's involvement in the peripancreatic vasculature. CT and magnetic resonance imaging (MRI) are the commonly used methods to evaluate vascular involvement; both were found to have similar sensitivities and specificities for diagnosis and vascular involvement in patients with PC [19]. During EUS examination, the relationships of the lesions to the coeliac trunk, portal vein confluence, and the superior mesenteric vein and artery are carefully assessed to determine operability. The accuracy of EUS in determining vascular invasion is similar to that of contrast-enhanced computed tomography (CECT), as reported by Bodea et al. [20]. They reported that when diagnosing superior mesenteric artery invasion, the accuracy of CECT and EUS were 84.92% and 87.39%, respectively. In diagnosing portal vein and superior mesenteric vein involvement, CECT had an accuracy of 84.83% and EUS had an accuracy of 92.17%. The accuracy of the two combined examinations in diagnosing vascular invasion was higher, reaching up to 93%.

Since 1995, several criteria have been proposed for their ability to diagnose malignant venous invasion using EUS. Although obstruction of a mesenteric vein and the resulting venous collaterals is a specific sign of unresectability, it is a rather insensitive parameter [21]. As an alternative, signs of venous wall invasion, such as "irregular wall," have been proposed as being sensitive (67–100%) and specific (100%) for malignant invasion of the mesenteric veins. Furthermore, increased blood flow velocity or on flow signal in the narrowed vascular cavity caused by the tumor invasion could also be revealed in the Color Doppler image.

In conclusion, according to the recently published meta-analysis, the sensitivity of EUS for vascular involvement is 87% with a very good specificity of approximately 90%. EUS appears to be particularly sensitive for detecting invasion of the portal and splenic veins.

12.3 EUS for Lymph Node Detection

EUS is considered a complementary tool to CT for N staging in PC. The sensitivity and specificity of EUS are only 62% and 74%, respectively.

In the EUS image, most of the malignant LNs (89.7%) were hypoechoic and with the cutoff value of 1.93, the sensitivity and specificity of the longitudinal to transverse ratio were 73% and 100%, respectively. The malignant LNs tended to be round in shape [22].

CE-EUS and elastography show potential to improve the accuracy of EUS for the differential diagnosis of begin and malignant lymph nodes [23–25] and may help decrease unnecessary biopsies [24]. Okasha et al. reported that the stain ratio cutoff value of 4.61 showed a sensitivity and specificity of 89% and 83%, respectively [26].

12.4 EUS-FNA

EUS-FNA is important in providing a pathological diagnosis of malignancy as well as in accurately staging the disease preoperatively. This influences the decision-making process and thereby reducing the morbidity that accompanies inappropriate surgical interventions in patients with advanced cancer. Today, the diagnostic ability of EUS-FNA is still improving, and the detection of PC currently has a sensitivity of 90–95% and specificity of 95–100% [5, 27–29]. It should also be noticed that CP has a significant impact on the diagnostic yield of EUS-FNA for PC. A study by Koshy et al. reported that the diagnostic yield decreased to 59.52% (compared to 78.75% without CP) when CP was present, and only the presence of calcifications was found to have an independent association with diagnostic yield [30].

For the abnormal lymph nodes of unknown origin, EUS-FNA has a high diagnostic value. According to Li et al., the pooled sensitivity and specificity of EUS-FNA for the diagnosis of lymphadenopathy are 94% and 98%, respectively [31]. In patients with PC, para-aortic lymph node (PALN) metastasis is considered to be a distant metastasis. Kurita et al. [32]. conducted a prospective study to compare the

diagnostic yield for PALN metastasis between EUS-FNA and PET/CT. They reported that preoperative EUS-FNA or PET/CT enabled a correct diagnosis in 20 (95.2%) and 12 (57.1%) patients, respectively; EUS-FNA had higher sensitivity and specificity for the diagnosis of PALN metastases (sensitivity 96.7%; specificity 100%) than PET/CT. Considering this result, they concluded that EUS-FNA should be part of the standard preoperative examination for patients with PC.

EUS-FNA can also occasionally contribute to accurate TNM staging in some other ways [33].

12.5 Peritoneal Tumor Dissemination or Malignant Ascites

Accurate diagnosis of peritoneal tumor dissemination or malignant ascites in PC may contribute to the selection of proper treatment options. EUS sometimes identifies ascites missed by other imaging methods. EUS-FNA may identify malignancy in a subset of patients and has the potential role for staging of cancer since the establishment of malignant ascites implies a more advanced stage of cancer [34–36].

12.6 Celiac Ganglia Metastasis Diagnosis

Metastasis to the celiac ganglia may upgrade the staging or impact the resectability. Malikowski et al. reported that celiac ganglia metastasis could be accurately distinguished from celiac lymph nodes using EUS [37] and safely identified with EUS-FNA [38]. However, the data still cannot prove that the survival of patients with celiac ganglia metastasis was different from the overall survival.

12.7 EUS-FNA in PC After Neoadjuvant Therapy

Ehrlich et al. reported the utility of EUS-FNA to determine surgical candidacy in patient with PC after neoadjuvant therapy [39]. In the series of patients with borderline resectable PC or locally advanced PC and persistent periarterial soft tissue cuffing after downstaging neoadjuvant treatment, EUS-FNA accurately determined surgical resectability and should be considered as part of the evaluation of such patients.

12.8 Limitations

The limited depth of penetration of the ultrasound waves of EUS prevents accurate assessment of structures that are located far from the ultrasound probe. EUS therefore has a limited role in the assessment of distant lymph nodes or metastatic disease. In cases where the anatomy is distorted or surgically altered, it may not be possible to obtain optimal imaging [40]. Thus, the assessment of tumor extension must be completed by performing CT or MRI [41, 42].

12.9 Conclusion

In conclusion, cross-sectional imaging techniques including CT, MRI, and PET-CT are commonly used for PC staging. However, EUS is a useful adjunct for accurate TN staging and evaluation of vascular invasion in PC in addition to allowing diagnostic tissue samples to be obtained. Furthermore, EUS is a reliable method for selection of patients with borderline resectable PC due to its high sensitivity and specificity for staging T3–T4 tumors.

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13 Endoscopic Ultrasound-Guided Fiducial Marker Placement for Stereotactic Body Radiotherapy (SBRT) of Pancreatic Cancer

Jeevinesh Naidu, Vinh-An Phan, and Nam Q. Nguyen

13.1 Introduction

Pancreatic cancer presents with surgically unresectable (locally advanced or metastatic) disease in 80% of patients [1]. In this group of patients, the standard of care is chemotherapy either with FOLFIRINOX or gemcitabine with nab-paclitaxel which provides a median survival of 6–8 months [2]. There is conflicting evidence on the benefit of radiotherapy in the treatment of pancreatic ductal adenocarcinoma (PDAC). Two initial randomised trials combined conventional external beam radiotherapy (EBRT) with 5-fluorouracil chemotherapy and demonstrated a survival advantage for resectable PDAC [3, 4]. However, the larger ESPAC-1 trial (2004) revealed a worse survival outcome in patients receiving combination therapy (10% vs. 20% 5-year survival rate, $P = 0.05$) [5]. It was hypothesised that the reason for this reduced survival was that EBRT caused toxicity to surrounding organs along with forcing the interruption of chemotherapy.

One approach to overcome this problem is to use marker-guided stereotactic body radiotherapy (SBRT), which has been recently applied in the field of radiation oncology. SBRT is a technique that requires image guidance to track motion of the tumour during inspiratory and expiratory respiratory cycles [6]. This is best achieved with the implantation of devices called fiducial markers. The potential advantage over conventional EBRT is the delivery of high doses of targeted radiation to the tumour with rapid dose falloff at the tumour periphery. Furthermore, since SRT can be delivered over a shorter duration, there is minimal interruption to chemotherapy.

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In order to minimize toxicity, SBRT has been used in combination with chemotherapy and early experience confirmed a survival benefit (median 11.15 months) with a comparatively low rate of adverse effects (22.3%) [7]. Recently, the use of neoadjuvant SBRT with chemotherapy in 159 patients with BRPC and LAPC downstaged the disease and allowed resection in 51% of patients, of which 91% had R0 resection margins. More importantly, grade 3 or greater toxicity occurred in only 7% of cases [8]. These recent studies have revived the interest in the use of combined chemoradiotherapy for the treatment of pancreatic cancer, especially with SRT as the preferred modality.

In summary, radiotherapy is undergoing a resurgence as an effective treatment strategy in patients with LAPC and BRPC. There is evidence for its advantage in a neoadjuvant and palliative setting due to good local control and low incidence of side effects. With many centres increasingly adopting SBRT, referrals for fiducial implantation are becoming commonplace. The aim of this chapter is to outline the benefits, methods, and outcomes of EUS-guided fiducial placement to assist treatment planning for SBRT in surgically unresectable, non-metastatic pancreatic cancer.

13.2 Role of Fiducial Placement in SBRT for Pancreatic Lesions

The main problems with treatment planning in SBRT are that (a) soft tissue is poorly visible on traditional computed tomography, (b) pancreatic lesions move together with the respiratory cycle, and (c) variation in the location of the tumour depending on the degree of distension of the GI lumen [9, 10]. Taken together, this makes a "moving, poorly visible target" without any fix bony landmarks to determine an accurate tumour margin to allow precise delivery of focus radiation.

In order to outline the margin of the targeted lesion, fiducial placement has been widely adopted in many tertiary centres. Fiducials are radiopaque markers of variable materials and sizes, which can be implanted into solid tumours either via the percutaneous (CT or US guided) route or via EUS [11]. Gold is the most commonly used fiducial as it is inert and has superior visibility compared to hydrogel and lipiodol. Using three-dimensional or four-dimensional CT software, the tumour margin and its surrounding organs can be delineated and tracked in real time, which allows variable doses of radiation to be delivered to different parts of the cancer (Fig. 13.1).

Another use for fiducial placement is in the marking of neuroendocrine tumours smaller than 2 cm in size prior to surgical resection. This has been reported in a few cases whereby intraoperative localisation of small NETs is challenging, and fiducial markers (or tattooing which will not be described here) allow intraoperative localisation to enable R0 resection margins to be achieved [12].

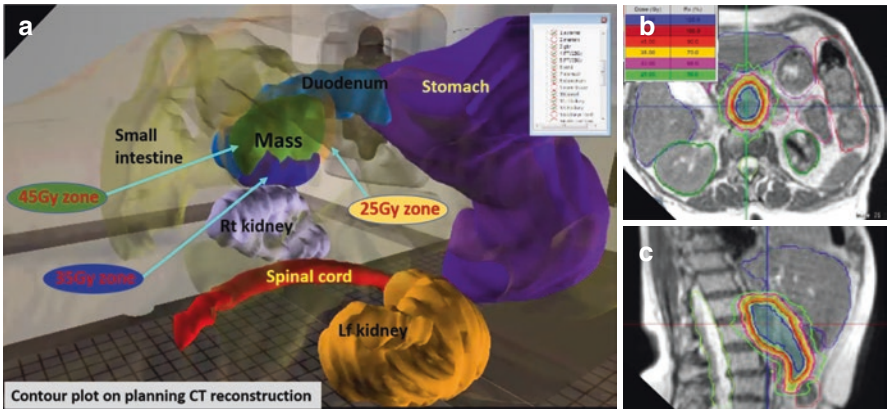

Fig. 13.1 Contour mapping and dosage delivery to the targeted cancer on 3D CT scan during preparation for SBRT. Simulated three-dimensional image on various angles and intensities of radiation beams targeting the tumour (**a**). Axial (**b**) and coronal (**c**) images of CT treatment planning. The colour borders around the lesion demonstrate the reduction of intensity from the centre of the lesion to the periphery reducing the potential damage to surrounding organs

13.3 Methods of Fiducial Placement

Laparoscopic: This method is infrequently adopted when the lesion is discovered as "unresectable" at the time of surgery. Before the closure of the abdominal wound, the tumour margin is marked by attaching fiducials to the surgical suture site intraoperatively. This approach has been shown to be superior in achieving ideal fiducial geometry (IFG) where the distance between two fiducials is 2 cm with a minimum fiducial angle of 15° to one another. However, IFG has not been shown to be important in the delivery of SRT and this will be described further below [13].

Percutaneous: Prior to the EUS-guided approach, percutaneous-guided approach via either US or CT was the most frequently used technique. In addition to the pancreatic lesion, this approach is also ideal for SBRT treatment of cancer locates in right liver lobe. For lesions in the retroperitoneal position of the pancreatic head and uncinate process, percutaneous approach can be technically challenging or impossible due to the overlying gas, which obscured the visualisation of the lesions. The complication is high with a 3.3% risk of bleeding and a 0.005% risk of tumour seeding along the needle path [11].

EUS-guided: Given the ability of EUS to access the pancreatic lesions, this approach is now the most widely used method for deploying fiducials in the pancreas and biliary tract. Not only it allows visualisation of the lesion in high resolution, EUS also provides a shorter distance from the needle puncture site to the lesion. These properties allow EUS to precisely define the margin of the cancer for marking, which is most relevant for small lesions that are not seen by conventional

imaging. Another advantage of EUS is that the Doppler function avoids major vascular structures and minimises the risk of bleeding and related complications. As a result, the risk of bleeding (1.8%) and tumour seeding along the needle track (only three cases reported thus far) are lower than those by percutaneous route [14].

13.4 Types of Fiducials for SBRT

Traditional gold (TG) fiducials are shorter and larger (5 mm in length × 1.2 mm in diameter) whereas flexible coiled (FC) fiducials are longer and smaller (10 mm in length × 0.35 mm in diameter) (Fig. 13.2a, b) [15]. The main advantages of smaller FC fiducials are increased flexibility and ease to load a 22G needle allowing easier extrusion of the needle when using a transduodenal approach. However, FC

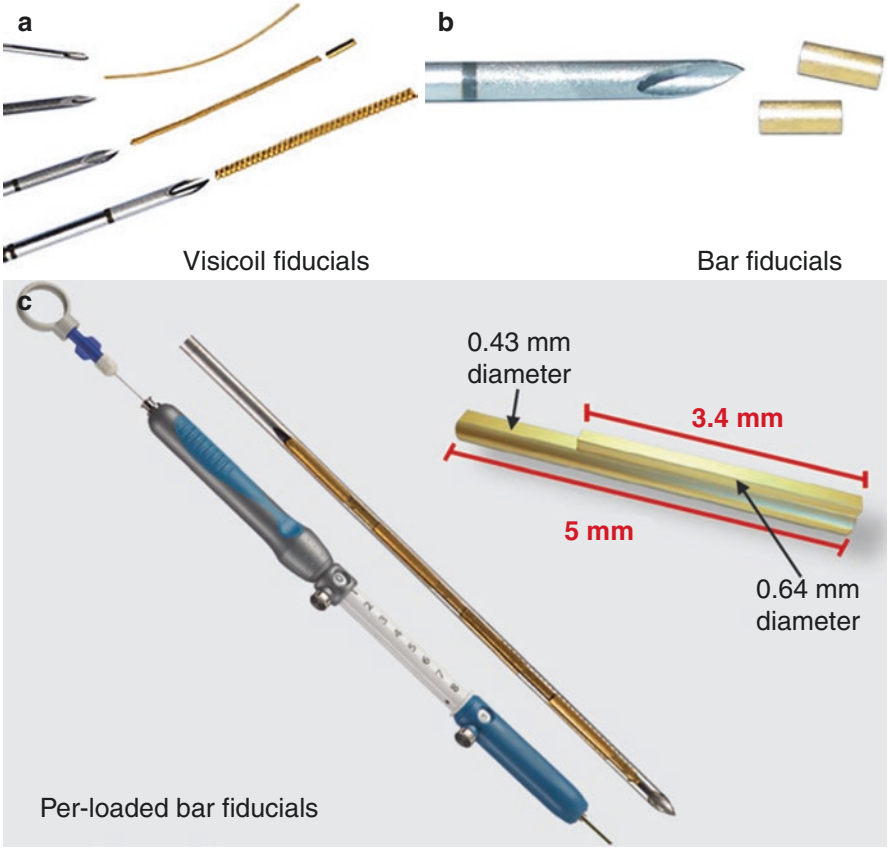

Fig. 13.2 Images of the available fiducials that are currently used in clinical practice, including coiled fiducials (**a**), bar fiducial (**b**), and a pre-loading bar-fiducial needle (**c**)

fiducials have a higher reported migration rate of up to 9% and reduced visibility compared to TG fiducials [16]. As such, the newer preloaded devices preferentially use smaller TG fiducials (5 mm × 0.43 mm) which can be loaded into a 22-gauge needle (Fig. 13.2c) [17]. The properties, advantages, and disadvantages of different types of fiducials are summarised in Table 13.1

13.5 Methods of Loading the Fiducial Needle

Whether the fiducials are inserted via percutaneous or EUS approach, the loading method of fiducials for insertion is similar. Each fiducial marker can be either front or back loaded into the needle prior to insertion.

1. *Back Loading:* The back-loading technique is most commonly used as it avoids pushing the fiducial through the entire length of needle, which can be difficult at times due to resistance. This involves preparing a fine-needle aspiration (FNA) delivery device prior to insertion into the accessory channel. This is done by withdrawing the stylet by 3 cm, pushing out the needle and inserting the fiducials in a retrograde manner using a catheter. Following insertion of the fiducials, the needle is pierced into bone wax to plug it and prevent loss of the fiducial while it is being advanced down the accessory channel (Fig. 13.3). The FNA needle is then injected into the tumour, and the stylet is inserted deploying the fiducial.

   A variation in the back-loading technique is the wet-fill technique in which the needle is immersed in saline, and a negative pressure is generated by withdrawing the stylet by 10 cm. The fiducials are then loaded retrograde into the needle without the use of bone wax seal and remain in place due to the surface tension of the saline. Deployment of the fiducial is achieved by full insertion of the stylet as above. The major drawback of this loading method is the risk of needle stick injury.
2. *Front Loading:* This technique involves inserting the FNA needle into the tumour using EUS guidance, removing the stylet completely then placing fiducial markers at the stylet opening. The stylet is then reinserted pushing the fiducial along until it is deployed in the tumour bed. Alternatively, instead of reinserting the stylet, small quantities of saline can be injected into the stylet port and used to flush the fiducial out into the tumour. The advantages and disadvantages between the two methods of fiducial loading are summarised in Table 13.2.
3. *Pre-loaded Fiducial Needles:* To eliminate the need for scope withdrawal and reloading a needle during the procedure, Cook™ and Medtronic™ currently manufacture preloaded fiducial delivery systems (Table 13.1). The Cook Echotip preloaded delivery system uses a 22G needle to deliver four gold bars (Fig. 13.2c) whereas the Medtronic Beacon system provides a 19-gauge or 22-gauge option preloaded with two gold bars to deliver fiducials of varying thickness [18].

Table 13.1 Comparison of the properties, method of deployment, advantages, and disadvantages between different types of fiducials

Fiducial type	Dimensions (mm)	Manufacturer	Method of deployment	Cost per fiducial unit (USD)	Advantages	Disadvantages
Cylindrical Gold Seeds	3–5 × 0.8–1.2	CIVCO Radiotherapy™	FL or BL using 19G needle	$43.60	Most experience, good visibility, low migration rate, cheap	Difficulty in deployment using 19G via transduodenal approach
Gold Anchor	10 × 0.28	Innomedicus Gold Anchor™	FL or BL using 22G needle	$130	Low migration rate	Difficulty deploying using FL approach (31.3% failure rate), expensive
Flexible coil	10 × 0.35	IZI Medical Visicoil™	FL or BL using 22G needle	$200	Transduodenal approach	Increased migration risk, less visibility
Gold Bar	5 × 0.43 5 × 0.43 5 × 0.75	Cook Echotip™ Ultra Medtronic Beacon™ Medtronic Beacon™	Preloaded 22G (4 fiducials) Preloaded 22G (2 fiducials) Preloaded 19G (2 fiducials)	$82.50/ fiducial $149/fiducial	No need to load needles thus reduced procedure time	Limitation to the number of fiducials per needle

FL front loading, *BL* back loading

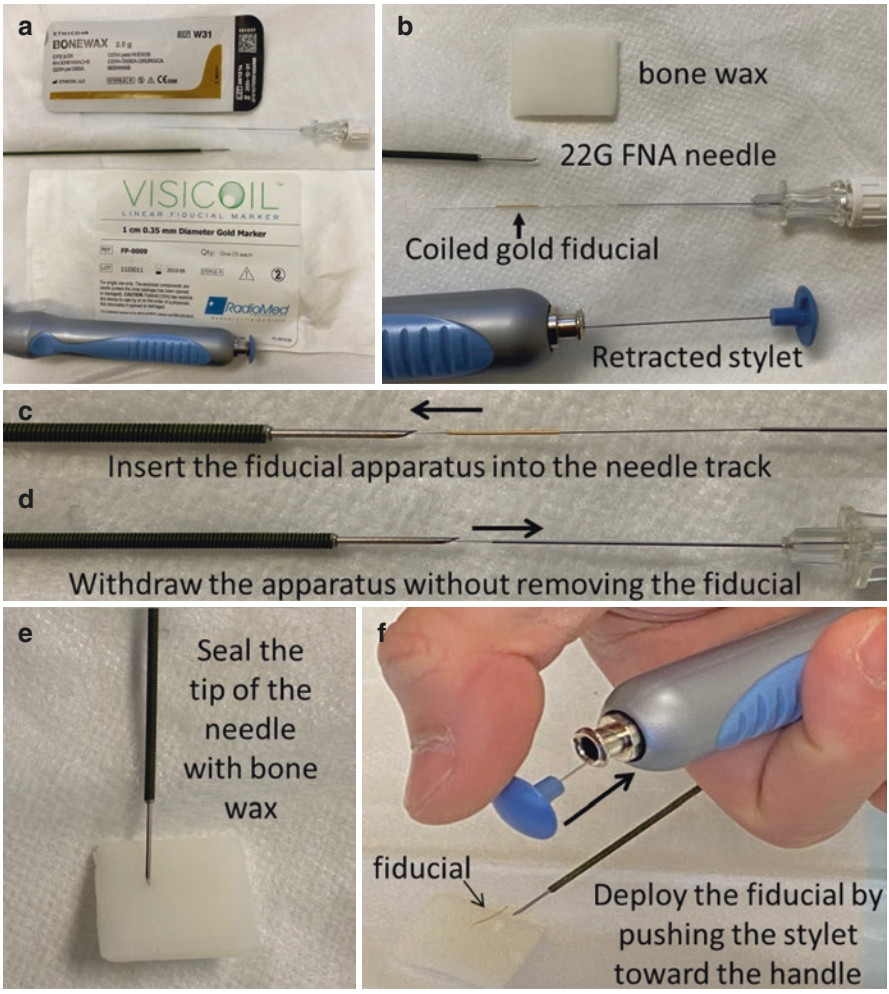

Fig. 13.3 Equipment and technique used in back-loading Visicoil fiducials for insertion of fiducial by EUS. The procedure requires a 22G FNA needle, a 1 cm 0.35 mm gold Visicoil and sterile bone wax (**a**, **b**). With the needle tip exposed for 1 cm and the stylet retracted for 5 cm, the gold Visicoil is loaded into the tip of the 22G needle by inserted the apparatus into the needle track with the tip of the needle face up (**b**, **c**). Once the gold Visicoil is completely inside the needle, the apparatus should be gently removed without pulling the gold Visicoil out (**d**). The tip of the needle is then sealed with steril bone wax (**e**). The needle tip is then retracted into the sheath, ready for the use by the EUS endoscopist. Once the needle tip is placed in the correct position within the lesion, the gold Visicoil can be deployed by pushing the stylet toward the handle (**f**). The expulsion of the fiducial into the lesion can be directly visualised under EUS

Table 13.2 Comparison of advantages and disadvantages of different loading methods of fiducial for insertion

Technique	Advantages	Disadvantages
Front loading	1. Does not need bone wax 2. Do not need to remove the needle to reload 3. Reduces the risk of needlestick injury	1. More technically challenging
Back loading (either bone wax seal or wet saline)	1. Relatively easy to use	1. Needle stick injury 2. Need to remove the needle from the accessory channel to reload 3. Needs bone wax which can lead to granuloma formation or cause failure of deployment due to plugging

13.6 Optimal Location to Place Fiducials for SBRT

The optimal placement of fiducials in relation to a pancreatic mass remains uncertain. The superiority of laparoscopically placed fiducials in achieving ideal fiducial geometry was previously described; however, this was not shown to lead to improved tracking and delivery of SRT [13]. In general, it is best to outline the main borders (medial and lateral) of the lesion, and if possible, its superior and inferior borders by fiducial placement (Fig. 13.4). Thus, at least two fiducials should be placed per lesion. For lesions larger than 4 cm, more fiducials may be required to delineate the extent of the lesion (Fig. 13.5). Our preference is to deploy fiducials within the lesion as opposed to along the outer edge to avoid the risk of migration, pancreatitis, or injury to adjacent organs.

13.7 Technical Outcomes of Fiducial Insertion in Pancreatic Lesions

Depending on the type of fiducial and size of the delivery needle, the technical success of EUS-guided fiducial insertion varies between 88% and 100% (Table 13.3). An initial experience with fiducial insertion using a 19G needle was 100% successful in nine patients by using a saline flush through the stylet port [19]. However, a subsequent larger study in 57 patients reported difficulties despite using this approach with success rates only reaching 88% [20]. This success rate, however, would reflect the real-life results as targeting lesions in the head, and uncinate process of the pancreas can be technically challenging when using a stiff 19G needle. By using a 22G needle and narrower traditional gold (TG) or flexible coil (FC) fiducials, the success rates in fiducial deployment transduodenally reached 100% [21]. Sealing the needle tip with bone wax reduced the problem of air bubble extrusion during fiducial placement obscuring

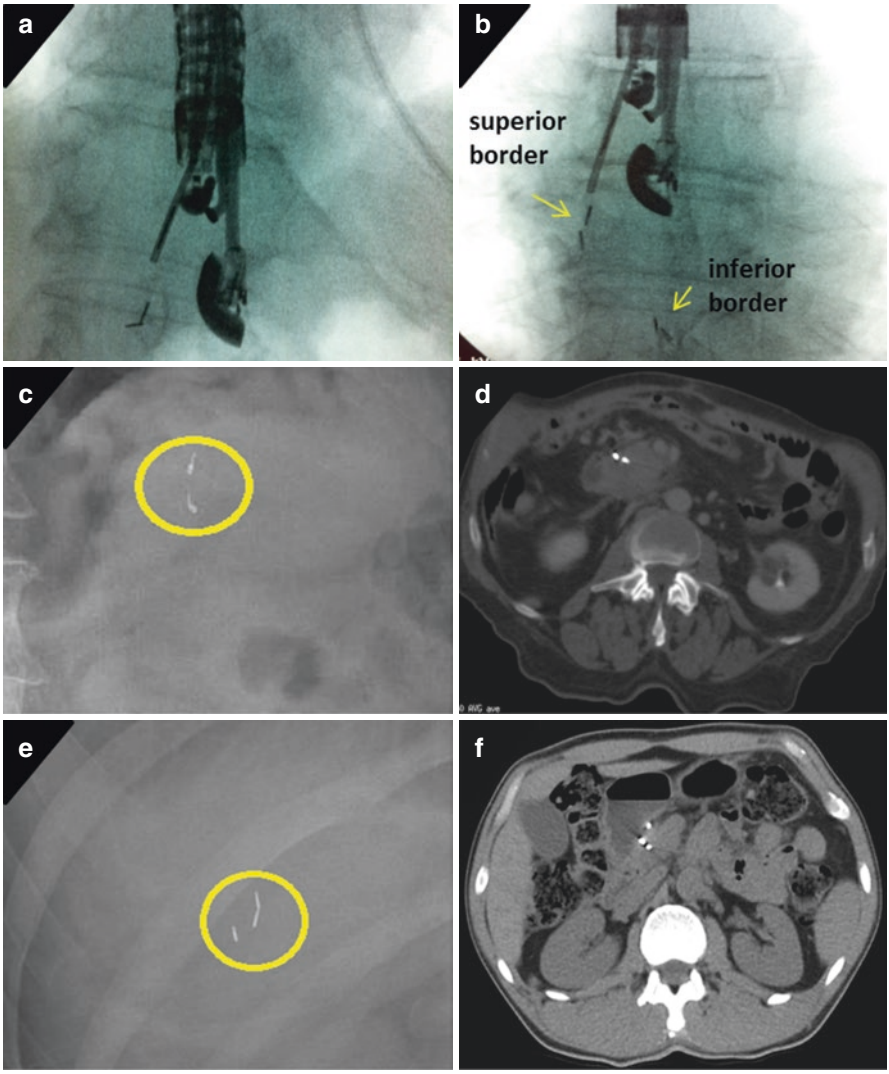

Fig. 13.4 Fluoroscopic appearance outlining the inferior and superior border of a pancreatic cancer using the pre-loaded bar fiducial 22G needle (**a**, **b**). Comparison of visibility of different types of fiducial marker, Visicoil (**c**, **d**) versus bar (**e**, **f**) fiducials, based on fluoroscopic (**a**, **b**) and tomographic assessments

the EUS view [22]. Although flexible coil fiducials have increased flexibility, there have been concerns regarding migration (up to 9% migration rate) and reduced visibility compared to TG fiducials [16, 17]. With greater experience, there was no longer a need for fluoroscopy, and multiple procedures were able to be performed in a single setting (FNB and coeliac plexus neurolysis) [22].

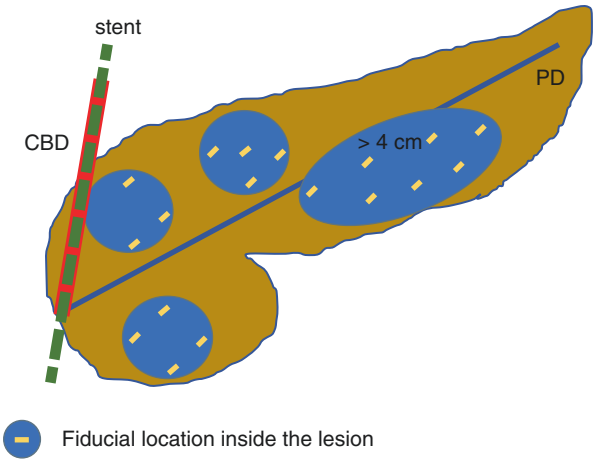

Fig. 13.5 Ideal configuration of fiducial placement within the pancreatic lesion for SBRT. The goal is to place 2–4 fiducials within the lesion to outline the borders of lesion on planning CT scan, providing a good mapping of the lesion for SBRT. Stent, either plastic or metal type, in the biliary tree can also be used a reference. For lesion in the body and tail of the pancreas, fiducials should be placed toward the posterior border of lesion to avoid outward migration. Avoid placement of fiducial within the pancreatic duct and inside the blood vessel. For lesions larger than 4 cm, more fiducials may be required to delineate the extent of the lesion

The development of preloaded fiducial needles has eliminated prior issues associated with back loading (time consuming, needle stick injury). These needles are preloaded with TG fiducials as opposed to FC due to superior visibility in patients with pancreatic cancer [17]. Our recent study [23] showed that a preloaded 22G fiducial needle (Cook Medical, USA) was associated with a shorter deployment time (0.94 vs. 5.5 min; P= 0.0001), greater fiducial number deployed (3.9 vs. 2.14; P = 0.0001), and was cheaper (USD$481 vs. USD$683; P = 0.001), compared to the use of a back-loaded 19G or 22G Echotip Ultra. In this study, the technical success was 100% in both groups.

In pancreatic neuroendocrine tumours smaller than 2 cm in size where surgical resection is indicated, the laparoscopic approach reduces the tactile feedback obtained by the surgeon intraoperatively. As such, localisation of a small lesion can be extremely challenging and EUS-guided fiducial placement is an option to aid enucleation of the lesion. Law et al. described two patients with a 7.4 mm uncinate lesion and a 9 mm neck of pancreas lesion whereby two FC fiducials were back-loaded onto a 22-gauge needle and injected into each patient successfully. Subsequent enucleation was successful with R0 resection margins [24]. Another case was described by Ramesh et al. whereby a 19-gauge needle was back-loaded with a single TG fiducial and successfully deployed into an insulinoma. This was easily identified in subsequent laparoscopic resection, and the patient had an excellent clinical outcome [12].

Table 13.3 Summary of published studies that evaluated the outcomes of different types of fiducials marking using EUS-guided approach

Article	*N*	Cancer	Needle	Fiducial	Technique	Fluoroscopy	Antibiotics	Technical success	Complications
Pishvaian et al. [26] (2006)	13	Pancreas, colon, oesophagus	19G	TG	FL	Yes	No	85% (11/13)	Cholangitis ($n = 1$)
Varadarajulu et al. [19] (2010)	9	Pancreas	19G	TG	BL	Yes	No	100% (9/9)	None
Park et al. [20] (2010)	57	Pancreas	19G	TG	BL—stylet push and hydrostatic	No	No	88% (50/57)	Minor bleeding ($n = 1$)
Dimaio et al. [27] (2010)	30	Oesophagus (18), pancreas (9), gastric (1), ovarian (1), cholangio (1)	22G	FC	BL	No	Not routine	97% (29/30)	Fever with elevated LFT ($n = 1$)
Sanders et al. [25] (2010)	51	Pancreas	19G	GS	BL	No		90% (46/51)	2% pancreatitis, 7% migration
Ammar et al. [21] (2010)	13	Pancreas (7), node (3), adrenal (1), cholangio (1), liver (1)	22G	FC	FL	No	No	100% (13/13)	None
Khasab et al. [17] (2012)	39	Pancreas	19G (29) 22G (10)	TG (29) FC (10)	BL	Mostly not	Yes	100%	None
Majumder et al. [13] (2013)	39	Pancreas	19G	TG	BL	No	Yes	90% (4 failed due to fiducial migration)	13% (5 patients); (3 abdominal pain, 1 vomiting, 1 mild pancreatitis)

(continued)

Table 13.3 (continued)

Article	*N*	Cancer	Needle	Fiducial	Technique	Fluoroscopy	Antibiotics	Technical success	Complications
Choi et al. [22] (2014)	32	Pancreas (29), liver (3)	19G	TG	BL	No	Yes	100%	3.1% (1 patient) migration, 3.1% pancreatitis
Davila Fajardo et al. [16] (2014)	23	Pancreas	22G	FC GA	BL	Not routine	Not routine	100%	9.5% migration, 4.3% (1 patient) bleeding, 4.3% cholangitis
Dhadham et al. [14] (2016)	514	Oesophageal (207), gastric (33), pancreas (188), rectal (103), others (32)	19G, 22G	TG, FC	BL	No	Not mentioned	99.8% (513/514)	1.4% migration (7 pts), 1.8% minor bleeding (9 pts)
Phan et al. [23] (2019)	60	Oesophago-gastric (27), pancreas (28), hepatic (5)	19G, 22G	FC, TG	BL, preloaded	No	Yes	100%	Cholangitis ($n = 1$)

13.8 Complications of Fiducial Insertion

Pancreatitis and bleeding are rare occurring in 2% and 1% of patients, respectively. Reported cases are mild requiring conservative inpatient management, and most patients were able to be discharged after 24–48 h [22, 25]. Cholangitis occurs in up to 4% of patients in two early studies where there was no routine administration of prophylactic antibiotics [26, 27]. Subsequent studies which implemented routine prophylactic antibiotic use reported no rates of cholangitis. As such, it is recommended that antibiotics be administered prior to fiducial implantation [28]. Our choice of antibiotics is either ciprofloxacin (400 mg IV stat) or ceftriaxone (1 g IV stat).

The accepted fiducial migration rate is between 1% and 4%; however, two studies reported high rates of 7% and 9.5% and will be discussed in greater detail. The rate of 9.5% was reported in a study that utilised Gold Anchor and Flexible Coil fiducials. Interestingly, the GA was more difficult to deploy (31.3% failure rate) whereas the FC fiducial was successful in all attempts. However, the high rate of migration happened exclusively with the FC fiducial in this study [16]. The risk of fiducial migration can be minimized by increasing the number of fiducials deployed to 3–4, allowing sufficient tracking during SBRT [25].

13.9 Conclusion

As SBRT is increasingly utilised for treatment of locally advanced pancreatic cancer, there is a greater demand for accurate outlining of the cancer by fiducial marking. Of the available modalities, EUS-guided fiducial insertion is the least invasive technique that is associated with very high technical success and a low complication rate. The advances in preloaded fiducial needle technology have further improved the safety, efficacy, cost, duration, and outcomes of the procedure.

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Endoscopic Ultrasound-Guided Therapies for Solid Pancreatic Tumors

14

Francesco Maria Di Matteo and Serena Stigliano

14.1 Introduction

Endoscopic ultrasound (EUS) has become an important interventional tool in the oncologic field based on the principle of EUS-guided puncture and thanks to the development of new technologies.

Local ablative techniques are emerging as complementary treatments in the multimodal strategy in pancreatic cancer especially for unresectable non-metastatic disease [1, 2].

Endoscopic ultrasound represents the perfect tool to guide local treatment of pancreatic lesions because it has the advantages of real-time visualization of the procedure and close contact of the probe to the target organ [3] compared to the ablation by a percutaneous [4] or intraoperative route [5], moreover with reduced morbidity compared with surgery.

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive tumors, along with a poor prognosis. Despite advancements in the multimodal approach, surgical resection still represents the only potentially curative treatment. However, more than 80% of patients are diagnosed at an unresectable stage.

Different chemo and/or radiotherapies have had poor results, with the 5-year survival rate at around 5–7% [6].

Pancreatic neuroendocrine neoplasms (pNEN) are rare tumors but their incidence has significantly increased in the last decades because of the widespread use of imaging studies [7]. They are classified depending on the disease stage and histological grade and, from a clinical viewpoint, based on the presence or absence of symptoms due to the secretion of hormones.

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The mainstay treatment of pNENs is surgery, which is associated with a significant benefit in terms of survival but is associated with important short- and long-term adverse events.

So, local therapy like EUS-guided ablation could be a valid alternative even in this setting.

Considering the mechanisms of action, EUS-guided ablation can be classified in two different approaches. The "direct mode" techniques have a locoregional effect on the lesion and include radiofrequency ablation (RFA), neodymium-doped yttrium aluminum garnet (Nd:YAG) laser ablation, cryotherm ablation, and ethanol injection. The other approach, the "indirect mode," consist in obtaining the antitumoral effect by a second mechanism, such as fine-needle injection of chemotherapeutic agents or immunotherapy factors (i.e., lymphocyte cultures) that stimulate the immune system against the lesion, or the placement of fiducial markers that guide stereotactic radiation [8].

14.2 EUS-Guided Direct-Mode Ablation

14.2.1 EUS-Guided Radiofrequency Ablation

RFA is a well-known procedure that produces coagulative necrosis induced by high temperature. It uses high-frequency alternating current as electromagnetic energy, which generates heat and results in coagulative necrosis.

The current available probe is the EUSRA RF electrode (STARmed, Koyang, South Korea) (Fig. 14.1).

It is a monopolar 18 and 19 G RFA electrode that is placed in the echoendoscope operative channel. It is 140 cm long with a sharp conical 1 cm tip for energy delivery. The needle is associated with an internal cooling system connected via a pump to an external cold saline solution source (0 °C) that prevents the charring of the tip and improves the ablation accuracy.

During the procedure, the needle electrode is passed under EUS guidance into the target lesion. The energy delivery is applied after confirming location of the tip of needle electrode within the margin of lesion on EUS. On activation, after variable seconds, echogenic bubbles gradually start appearing around the needle, indicating RFA at the site (Fig. 14.2).

On histology after RFA, three areas can be distinguished depending on proximity to the probe. The central area has coagulative necrosis due to direct contact with the probe. The transitional area has sublethal damage due to the thermal conduction of the central area; cell apoptosis or complete healing is possible. The healthy external area is unaffected by the ablation.

By now, three studies have evaluated the feasibility and safety of EUS-RFA in patients with locally advanced pancreatic ductal adenocarcinoma.

In 2016, Song et al. [9] conducted a study on six patients with a histologically confirmed pancreatic cancer, at unresectable stage due to locally advanced or metastasis disease, and resistant to previous treatment modality. They showed that

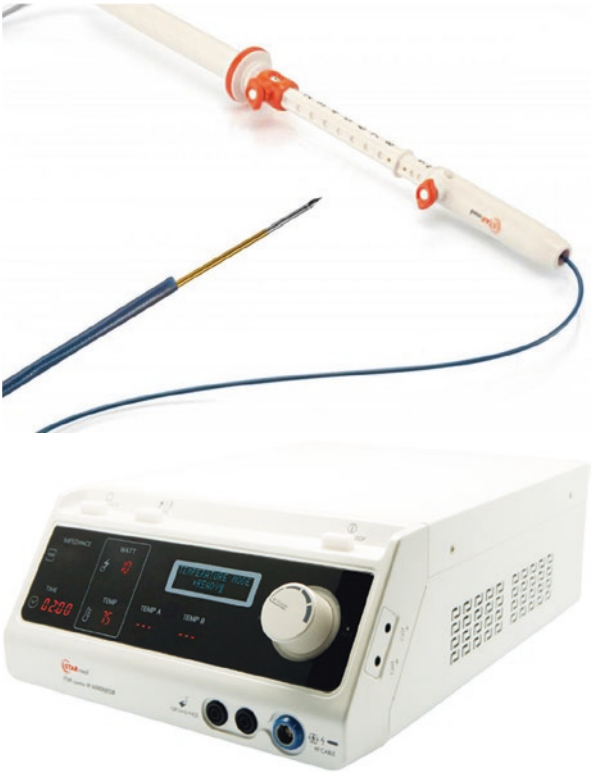

Fig. 14.1 EUSRA RF electrode (STARmed, Koyang, South Korea) with a 10-mm active tip. The handle is connected to the water-cooling device and to the VIVA RF generator

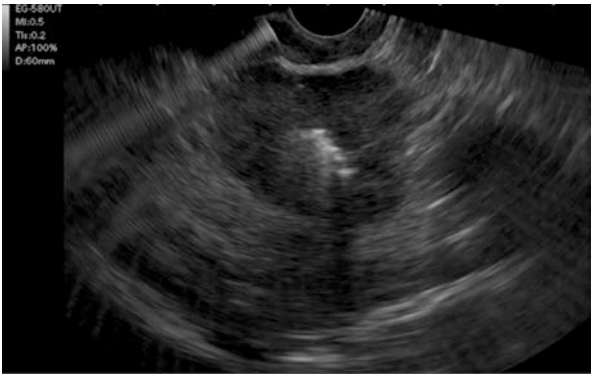

Fig. 14.2 EUS-guided radiofrequency ablation on pancreatic ductal adenocarcinoma

EUS-RFA was performed successfully on all patients with no major adverse events (pancreatitis, bleeding, duodenal injury, or portal vein and/or splenic vein thrombosis). There was no procedure-related mortality.

Same results were observed in another study [10] conducted on ten patients with unresectable nonmetastatic cancer. In this study, the secondary end point was also to evaluate the presence of necrosis within the neoplastic tissue as effect of the

ablative procedure. At contrast-enhancement CT scan, radiological response was defined as the presence of a well-defined hypodense intra-tumor area compared to the surrounding neoplastic tissue.

Recently, Crinò et al. [11] showed their results of a study conducted on eight patients with PDAC, nonresectable and nonmetastatic after first-line chemotherapy and/or radiotherapy or resectable but not suitable for surgery due to the patient's comorbidities. Again, technical success was defined by achieving tumor ablation (i.e., the presence of a markedly hypodense area inside the tumor that was detectable at the day after CECT scan). The volume of the ablated area (and its percentage compared to the original tumor volume) was calculated. An ablated area in the tumor was obtained in all patients. About the adverse events, only three patients experienced mild abdominal pain after the procedure.

These results confirmed that EUS-RFA is feasible and safe, demonstrating its ability to produce substantial necrosis at the ablation site. However, the exact role of EUS-RFA in PDAC management must be further assessed.

About the EUS-guided RFA ablation for pNEN, few case reports and two case series have been published. Choi et al. [12] treated seven patients with a median tumor diameter of 20 mm, and a radiological complete response was achieved in five patients. Regarding adverse events one, patient developed abdominal pain and one developed mild pancreatitis. In a second series by Barthet et al. [13], 12 patients with 13 nonfunctional pNEN lesions <2 cm were treated with EUS-RFA. At 6 months, complete response was achieved in nine lesions (71%). Adverse events were observed in two patients, with one case of pancreatitis and one case of main pancreatic duct (MPD) stenosis.

Recently, Oleinikov et al. assessed the feasibility, efficacy, and safety of EUS RFA in patients with functional and nonfunctional pNET, showing a complete radiological response in 96% of lesions. Adverse events were observed in two patients, both mild acute pancreatitis [14].

14.2.2 EUS-Guided Laser Ablation

Laser ablation is a minimally invasive method that works by directing low-power laser light energy into the tissue. The use of thinner laser fibers enables insertion into standard EUS needles (i.e., 22 G) and their potential application in deep abdominal organs, such as the pancreas.

The available device is a 1064-nm wavelength neodymium-yttrium aluminum garnet (Nd:YAG) laser light (Echo-laser; Elesta s.r.l., Florence, Italy) that is used with the insertion of a 300-mm optical fiber (Elesta s.r.l.) in a standard EUS needle (Fig. 14.3).

Up to now, preliminary studies in an in vivo animal model have demonstrated the efficacy and safety of laser ablation with Nd:YAG laser [15].

Recently, this minimally invasive laser has been used for the treatment of a neuroendocrine pancreatic tumor in human. Laser ablation under EUS guidance was performed using Nd:YAG laser at 4.0 W for 300 s and no complications occurred

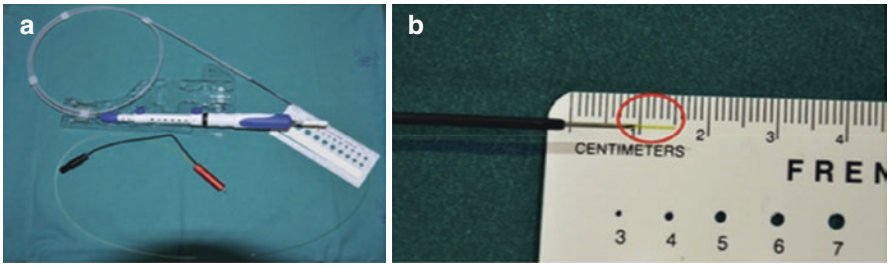

Fig. 14.3 (**a**) A 22-gauge Needle Flex from Boston Scientific preloaded before the procedure. (**b**) The fiber out from the tip of the needle (5 mm)

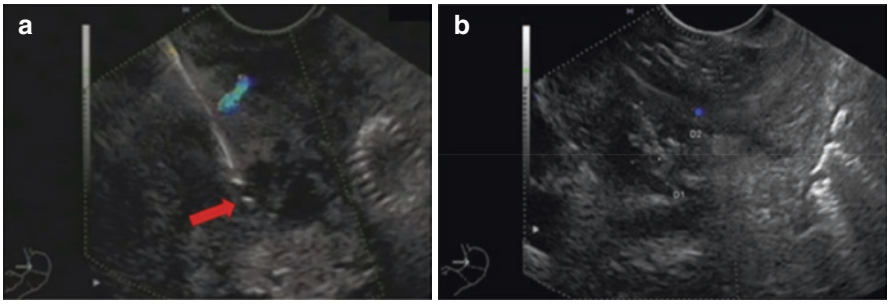

Fig. 14.4 (**a**) The hyperechoic spot visible at 5 mm from the tip of the needle inside the tumor (red arrow). (**b**) At the end of the procedure, EUS showed a hyperechoic area along the path of the probe surrounded by nonhomogeneous tissue with hyperechoic spots

during the procedure (Fig. 14.4). A well-defined coagulative necrotic area at the posttreatment CT scan was observed, and no metabolic activity was seen at a 6-year follow-up [16].

Furthermore, the same group assessed the feasibility of EUS-guided laser ablation for unresectable pancreatic cancer. The procedure was feasible in all cases, and no major adverse events were recorded. The lowest effective power settings were applied to avoid potential damage to the adjacent normal parenchyma. According to the results of this human application, the power setting 4 W/1000 J achieved the largest ablation volume without clinical adverse events. Median post-LA survival of the patients was 7.4 months (range, 29–662 days) [17].

14.2.3 EUS-Guided Cryotherm Ablation

Cryotherm ablation is a hybrid bipolar technique combining the thermal injury of RFA with the cooling effect of a cryogenic gas.

The currently available probe was developed by ERBE Elektromedizin GmbH (Tübingen, Germany) (Fig. 14.5). This probe uses an EUS-FNA needle with a sharp distal tip containing two interstitial electrodes that form the current closed system

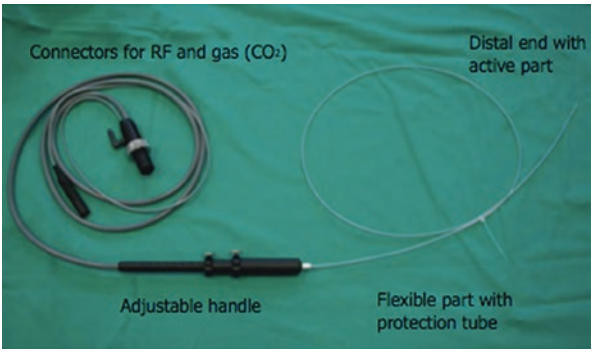

Fig. 14.5 The ERBE flexible probe covered with a protection tube can be passed through the operative channel of the echoendoscope

Fig. 14.6 Hybrid cryotherm probe (14 G) ("Hybrid-Therm"; ERBE, Tubingen, Germany)

(Fig. 14.6). The electrically active section is 26 mm long with a gauge of 1.8 mm. A Teflon sheet covers the device, and it can easily pass through the operative channel of a therapeutic EUS scope once the tumor has been detected. The probe is connected to the energy generator and the CO_2 source.

A bipolar system is believed to create ablations with less collateral thermal damage than monopolar systems. In addition, combining the effects of the two technologies, this device increases the effects of the two approaches and overcomes the disadvantage of less efficiency [8].

The feasibility and efficacy of EUS-guided cryotherm ablation was first demonstrated in animal model [18] and in ex vivo study [19] on neoplastic tissue of explanted pancreas from patients with resectable pancreatic adenocarcinoma.

The histological examination found a positive correlation between the size of the ablated area and the application time.

Arcidiacono et al. evaluated the feasibility and safety of cryotherm ablation in patients with locally advanced PDAC. The treatment was feasible in 72.8% because fibrosis and desmoplastic reaction of the lesion and gastroduodenal wall blocked the probe insertion. No severe complications were reported during or immediately after the procedure. The study showed a direct correlation between application time and the treated area [20].

In addition, besides the local tissue ablation, a systemic inflammatory response to cryoablation has been postulated as a reaction that can lead to an antitumor response, not only in the treated area but also in distant metastasis [21].

14.2.4 EUS-Guided Ethanol Ablation

Ethanol is a low viscosity chemical agent that determines coagulative necrosis with subsequent fibrosis, small vessel thrombosis, and granulomatous tissue formation.

It can be injected through a small gauge needle under EUS view.

Several studies have shown that EUS-guided ethanol injection is a safe and effective procedure in several pancreatic neoplasms, such as cystic lesions and neuroendocrine tumors [22–24].

In a recent study, Paik et al. evaluated the efficacy of EUS-guided ethanol ablation of solid pNEN. They showed that the procedure achieved a treatment success rate of 75% with one major adverse event (severe acute pancreatitis) [25].

About the efficacy of EUS-guided ethanol ablation in PDAC, Facciorusso et al. compared the efficacy and safety of EUS-guided ethanol ablation combined with EUS-guided celiac plexus neurolysis (EUS-CPN) with EUS-CPN alone for pain management, ablation rate of the tumor, and the overall survival. Ablation was confirmed in 84.6% of patients treated with the combined approach, and as a result of the direct tumor killing activity of ethanol, median overall survival was significantly longer after the combined therapy (8.3 vs. 6.5 months; $P = 0.05$) [26].

14.3 Local Ablation and Immunomodulation

The observation that spontaneous regression of untreated tumors can occur after the ablation of distant tumor masses may indicate an involvement of immune activation after the thermoablation [27].

Although the sequential mechanisms involved are not yet fully elucidated, several pieces of the puzzle have been identified; thermal treatment induces necrosis and can lead to local inflammation, release of danger signals like heat shock proteins (Hsp), which may even be detected systemically. This stimulates the recruitment and activation of immune effector cells, including dendritic cells, near and most probably inside the damaged tumoral tissue. These cells activate antitumor adaptive immunity, including CD4+, CD8+ T cells, and antibody production, which can contribute to local tumor elimination, control distant tumors including micrometastases, and establish long-lasting antitumor immunological memory [28, 29].

It is supposed that controlling the induction of physiological stress, the local ablation offers the possibility of letting the "natural" immune response develop by breaking self-tolerance. So, thermal ablation of cancer provides a therapeutic implementation of the *danger model*. However, the induced antitumor immunity is weak and probably not sufficient alone to eradicate established tumors, but it can synergize with some chemotherapies and immunomodulating strategies [30, 31].

14.4 EUS-Guided Indirect Mode Ablation

Many novel therapeutic agents and techniques delivered with EUS fine-needle injection (EUS FNI) have been used in clinical trials for the treatment of advanced pancreatic cancer [32].

One example is the use of an allogeneic mixed lymphocyte culture, termed cytoimplant. Chang et al. [33] completed a phase I trial in which the cytoimplant was generated from a culture of healthy donor and patient's peripheral blood mononuclear cells. There were no procedure-related complications. Tumor response was evaluated by computed tomography; two patients had a partial response (i.e., more than a 50% decrease in cross-sectional area), one had a minimal response, three had no change, and two had a progression of the disease.

Another type of injectable agents is the TNFerade (GenVec Inc., USA). It is a replication-deficient adenovirus vector that carries the human tumor necrosis factor-alpha gene regulated by a radiation-inducible promoter (Egr-1). Hecht et al. [34] reported three cases of partial response, one case of complete response, and 12 cases of stable disease (median survival of 297 days). However, another large randomized multicenter phase III study [35] involving 304 patients reported no survival benefit of adding intratumoral TNFerade injection to 5-fluorouracil and radiotherapy compared with chemotherapy alone.

A new antitumor agent is the ONYX-015 (Onyx Pharmaceuticals, USA) [36]. It is an oncolytic attenuated adenovirus that preferentially replicates in malignant cells, leading to cell death. Hecht et al. [37] completed a phase I/II trial of EUS FNI-guided intratumoral delivery of ONYX-015 combined with gemcitabine in 21 patients with advanced pancreatic carcinoma. No convincing efficacy for ONYX-015 was found: 2 with partial regression; 2 with minor progression; 6 with stable disease; and 11 with progressive disease or treatment-related toxicity.

However, in view of the above suboptimal results, the attention has been turned in other fields of the cancer treatment such as the nanotechnology.

Nanotherapies may hold the key to reduce the damage of the adjacent healthy tissues and limit other side effects of cytotoxic agents by encapsulating drugs into a nontoxic nanoformulation that can pass through immunogenic and stromal barriers. Nanotherapies could really target the drug with high specificity to the tumor site, leading to improvement of the survival rate of patients with pancreatic cancer. This is a very interesting, still poorly exploited field and even more studies are focusing in this research filed [38, 39].

14.5 Conclusions

Endoscopic ultrasound-guided ablation represents a feasible, safe, and effective tool for the treatment of unresectable pancreatic solid tumors or for patient unfit for surgery.

Several different EUS-guided ablative techniques have been introduced and the current experience shows good results.

This technique must be considered in a multistep scenario, complementary to systemic chemotherapy or radiotherapy. Indeed, it seems to play an important role not only in producing a local destruction of the tumor but also in changing its molecular profile and its microenvironment, inducing different susceptibility to chemotherapy. Furthermore, the local ablation of the tumor can induce the activation of the immune system and contribute to local tumor elimination, control distant tumors including metastases, and determine long-lasting antitumor immunological memory.

However, up to now, the available studies are conducted on small number of patients. Prospective randomized controlled trials are awaited to accurately evaluate its efficacy in terms of survival and quality of life.

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Endoscopic Ultrasound-Guided Pancreatic Cysts Ablation

15

Nico Pagano and Claudio Ricci

Key Points

- Pancreatic cystic lesions are still a difficult subject.
- Correct classification and diagnosis of cystic lesions are not always easy.
- Risk stratification of neoplastic cysts has an ample gray area.
- Current strategies are only follow-up or surgery, both carrying risks.
- Cyst ablation techniques have been tested in the last years and seem to have good results and acceptable risk profile.
- We know nothing about long-term results and the real impact on pancreatic cancer incidence reduction in these patients.

15.1 Introduction

Pancreatic cancer is increasing in incidence and is one of the most lethal malignancies in the world [1]. Up to one out of five cases of pancreatic cancers develop from mucinous cysts, which are increasingly diagnosed, mostly as incidental finding, during cross-sectional imaging [2, 3]. Since the cysts' incidence increases in the older population and the technological development improves the sensitivity of CT scan and MRI, we are experiencing an epidemic of pancreatic cystic lesions. This burden of cases is critical for the health systems since the follow-up is expensive, and the decision to operate a cyst is quite tricky, considering the high morbidity and mortality of pancreatic surgery. Not all cysts are to evolve in malignancy, but it is often challenging to provide an accurate estimation of the risk, discerning between the non-evolutive ones and the potentially malignant [4]. The mucinous cysts bear a potential of malignant transformation, and, among this sub-type, certain features suggest an increased risk. Gastroenterological associations produced various

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guidelines to aid the clinician during daily work in discerning the patients that need intervention and state the timing of follow-up for the others [5]. A mucinous cyst has an overall risk of progression to malignancy that ranges between 1 and 25% [6]. With current imaging and fluid analysis techniques, the probability of transformation in every single cyst is a rough estimate. Even molecular analysis, a costly technology, has not been validated as a reliable parameter in predicting future malignancy [7]. These strategies are often inadequate because, despite all efforts, most cystic lesions lay in the gray area of intermediate risk.

At present, however, there are no options against potentially malignant pancreatic cysts, except surgery or a strict follow-up, both bearing risks. In fact, on the one hand, operating a pancreatic cyst exposes the patient to a high risk of mortality and morbidity; on the other hand, follow-up is imperfect in promptly detecting malignant transformation, is costly, and represents a psychological burden for the patient.

We are here in a similar setting as Barrett esophagus; before the advent of ablation techniques, the only available options for this condition were surveillance and surgery, both limited and risky.

In the last years, various reports of pancreatic cysts ablation with EUS guidance have been published, paving the way for a possible change in paradigm [8].

Experimenting with methods to reduce the risk of malignancy, like a local treatment of pancreatic cysts, may provide a new weapon in the battle against pancreatic cancer.

15.2 Technique

The procedure of pancreatic cyst ablation is technically an EUS-FNA, with all the same requirements as sedation, patient information, and devices [9]. There is an indication for antibiotic prophylaxis, according to guidelines on FNA in pancreatic cysts [10]. The lavage agent used and the chemotherapeutic infusion must be ready before starting the procedure, and a close cooperation with the oncologist is recommended for the preparation of chemotherapeutic agents and the subsequent disposal. A thorough evaluation of the lesion, including contrast-enhanced EUS, is mandatory. For what concerns the treatment of the cyst, the endoscopist inserts the needle using a standard FNA technique aspiring the full content of the cavity. The choice of the needle relies on the content of the cyst; a more viscous liquid requires the use of a 19-gauge needle to facilitate the evacuation, while in less viscous content, a 22-gauge needle may be adequate [11]. After the evacuation of the content, ethanol lavage involves alternative alcohol injection and aspiration in the cyst for up to 5 min [12]. The endoscopist injects the same amount of alcohol as the quantity of liquid aspirated from the cyst. In the alcohol-free approach, after the aspiration of the fluid content, the cystic cavity is filled with a chemotherapeutic agent or a cocktail of agents. As in the ethanol lavage, the amount of liquid infused must be the same as the one aspirated. The solution of paclitaxel is more viscous than ethanol, so that the infusion needs a higher pressure. An infusion device or a high-pressure gun is often necessary to inject the solution. As opposed to ethanol lavage,

paclitaxel is left in place to produce its effect for a longer time [13]. One typical trick is to leave a little amount of liquid surrounding the tip of the needle to create a safety cushion and avoid spillover outside the cystic wall [14].

In the case of multilocular cysts, ablation may be more problematic because a single puncture may not be enough to inject the solution in all the compartments, and multiple punctures may be required. The multiple puncture approach increases procedure length, costs, and risks [15]. Expectedly, unilocular cysts have better outcomes than multilocular cysts and cysts smaller than 35 mm have better responses than larger cysts [16].

Data seem to show better results with repeated procedures, and some authors proposed a scheduled control at 3 months with retreatment of lesions still larger than 15 mm at the second evaluation, although to set the best timing we need further data [17]. Various authors stated the parameters for evaluating the response to treatment. The current definition of complete response is a reduction of the cystic size of more than 95% from baseline. A partial response is a reduction between 75 and 95% of the size. A reduction of less than 75% is a nonresponse [18].

15.3 Chemotherapy and Ethanol

The concept of local application of chemotherapy or toxic substances to treat tumors is an old one [13]. This approach aims at minimizing the systemic toxicity of chemotherapy and increases the dose within the tumoral tissue. Ethanol was the first substance used in the local ablation therapy of various tumors, like hepatocarcinoma and other types of lesions [19]. Due to its toxic effect, the alcohol creates tissue damage, obtaining the reduction or the complete ablation of the neoplastic tissue. Unfortunately, local ethanol toxicity is, at the same time, its strength and its limitation. In the very delicate pancreatic parenchyma, the local effect of alcohol creates damage to the adjacent healthy tissue, often resulting in pancreatitis [20]. Besides, damage of the neoplastic epithelium of the cyst is often incomplete and non-uniform [21].

Paclitaxel is a chemotherapeutic agent that inhibits microtubule-dependent cell processes, causing cessation of cell division and apoptosis. Due to its high viscosity, the substance exerts a long-term effect inside the cystic cavity [22].

Gemcitabine has a role in the treatment of pancreatic cancer. The results of the studies on local ablation suggest that this drug has a synergistic effect with paclitaxel in treating pancreatic neoplastic cysts [11].

15.4 Radiofrequency Ablation

Radiofrequency ablation (RFA) is a new technology used to treat tumors in different sites. RFA uses electromagnetic energy and high-frequency alternating currents to produce coagulative necrosis when applied to tissues [23]. Lately some authors proposed the use of RFA to treat pancreatic cystic lesions.

15.5 Available Data

The first report of EUS-guided cyst ablation was by Gan et al. In this work, endoscopists, after aspiration of the cystic liquid, injected an 80% alcohol solution in pancreatic cysts, leaving it in place for up to 5 min [24]. The follow-up showed a 35% complete response rate with no adverse events. After this first experience, results were confirmed by a prospective randomized trial, which reported 5% of pancreatitis after the procedure [16]. The majority of the following studies were nonrandomized and provided similar results [25]. More recently, a prospective trial failed to produce the same results reporting a much lower rate of complete ablation and a 4% incidence of post-procedure pancreatitis [26].

As described in Table 15.1, more than 200 patients underwent EUS-guided pancreatic cyst ablation with ethanol. Half of the treated cysts were unilocular, and the other half had some septa. The majority of the cysts were mucinous (either IPMN or mucinous cystadenomas), but 20% were serous cystadenomas, and the remaining were undetermined or even pseudocysts. The range of cystic lesions size was 19–30 mm. One-third of the cysts had a complete response to treatment, and the complication rate was about 20%. Among the reported complications, abdominal pain was the more frequent one with a rate of up to 15%, and pancreatitis occurred in 2% of the patients. One intracystic bleeding was observed (0.5% of patients).

Although promising, because of the low-resolution rate and the relatively high-complication rate, ethanol lavage has not entered clinical practice. The further technical evolution of the procedure was the intracystic injection of paclitaxel after ethanol, as reported by Oh and colleagues [27]. The experience with this technique showed better results than ethanol alone, leading to an ablation rate of up to 80%. This resolution rate is more acceptable for application in clinical practice, but the significant rate of adverse events, particularly acute pancreatitis, represents a severe limitation to the diffusion of the technique. Besides, other critical adverse events have been reported, like peritonitis and venous thrombosis. Because the main problem is the toxicity of ethanol, some authors had the idea to try an alcohol-free technique. The CHARM trial was the first to explore a chemoablation approach without alcohol [28]. The study compared two arms, both using chemotherapeutic lavage,

Table 15.1 Studies on EUS-guided pancreatic cystic lesions ablation with ethanol

Authors	Design	nr pts	Remission rate (%)	Adverse events rate (%)
Gan et al. [24]	Prospective (pilot)	25	35	0
Dewitt et al. 2009 [36]	RCT	42	33	24
DiMaio et al. [17]	Retrospective	13	38	8
Caillol et al., 2012 [37]	Retrospective	13	85	0
Gomez et al., 2016 [21]	Prospective(pilot)	23	9	8
Park et al., 2016 [12]	Prospective	91	37	14

preceded by ethanol lavage in one group and saline in the other. In the follow-up at 12 months, there was no difference in the rate of complete ablation between the two groups. In this trial, both groups had a complete response rate of over 60%. This result likely relies on the design of the study because the authors used an intracystic cocktail of two chemotherapic agents: gemcitabine and paclitaxel. The other main result is the significantly lower rate of adverse events in the alcohol-free arm. Future larger trials will test the technique in a larger number of patients.

Table 15.2 includes studies on chemoablation with paclitaxel-based regimens. More than 300 patients underwent the treatment. The mucinous cysts were again the majority being more than 50% but, again, about 10% of the cysts were serous cystadenoma. The size of the cysts ranged between 24 and 32 mm. More than 60% of cysts had complete resolution. Complications occurred in 15% of patients with 5% of pancreatitis. Splenic vein thrombosis, pancreatic duct stricture, portal vein thrombosis, a spillover of liquid in the pericystic space were rare complications (under 0.5%).

In synthesis, data show a higher rate of response with chemoablation regimens compared to ethanol alone with a lower rate of adverse events but, in both groups, not all the cystic lesions were mucinous, thus generating some concerns about the results.

Available data advice against the use of ethanol for cyst ablation: different agents with a better tolerability profile and a higher rate of ablation should be preferred. Regarding the long-term response, the most extended follow-up is reported by Choi with a sustained remission of over 98% at 6 years in patients who achieved complete cyst ablation [30].

Recently, a panel of experts produced a position statement on EUS-guided pancreatic cyst ablation, exploring the subject and considering various vital points [31].

Regarding the indication, this procedure may apply to patients that have uni or oligo-locular mucinous cysts who are excluded from surgery for various reasons. The cutoff for the treatment should be a size of more than 2 cm in a growing cyst or a diameter larger than 3 cm.

Experts recommend a thorough examination of the lesion with all the available methods, including CT scan, MRI, and contrast-enhanced EUS. Treatment should apply to the neoplastic cysts, excluding benign ones and pseudocysts. Cysts with a

Table 15.2 Studies on EUS-guided pancreatic cystic lesions ablation with ethanol or saline + chemotherapeutics (paclitaxel and gemcitabine)

Authors	Design	nr pts	Remission rate (%)	Adverse events rate (%)
Oh et al., 2008 [40]	Prospective	14	79	21
Oh et al., 2009 [41]	Prospective	10	60	10
Oh et al. [27]	Prospective	47	62	4
DeWitt et al. [29]	Prospective	22	50	23
Moyer et al. [28]	Prospective	39	67	28
Kim et al., 2017 [39]	Prospective	36	56	16
Moyer et al. [28]	Prospective	39	67	28
Choi et al., 2017 [38]	Prospective	164	72	15

size greater than 6 cm are poor candidates for the treatment, given the low probability of response in this group of lesions. Patients with a dilated pancreatic duct measuring more than 5 mm are not candidates for treatment as patients with clear signs of solid malignancy or a history of acute pancreatitis. Other contraindications are pregnancy, nonreversible coagulopathy, and severe pancreatic atrophy due to pancreatic duct stenosis. Experts advise the use of a 22- or a 19-gauge needle for the ablation procedure. The recommendation is to use antibiotic prophylaxis with the same rules and regimens used for EUS-FNA of cystic lesions. The use of ethanol does not seem to add any advantage in the case of chemoablation of cystic pancreatic lesions. The panel concluded that the results in terms of remission should rely on the measurement of cystic size with a complete response defined as a reduction of more than 95% of the cystic radius.

The procedure carries the same baseline risk of EUS-FNA of a pancreatic cyst, providing that a trained endoscopist performs it.

There are few studies about the application of RFA in the treatment of pancreatic cystic lesions. The first experience on EUS-guided RFA ablation was on six patients with a complete resolution in two patients and a partial response in three patients. Two patients reported abdominal pain [32].

A subsequent study on 30 patients was designed to evaluate safety as primary outcome. The study included mucinous lesions and cystic neuroendocrine tumors with 1 year of follow-up. The adverse events rate was 10%, including acute pancreatitis with jejunal perforation, occurring in the first two subjects enrolled. The protocol was modified after the first two patients and included prophylaxis for infection and perforation. No other adverse events occurred except a pancreatic duct stenosis which was treated by ERCP. Regarding efficacy, at 12 months, 86% of neuroendocrine lesions and 65% of cysts showed complete resolution [33].

15.6 Conclusions

Management of pancreatic cystic lesions is still matter of debate but, undoubtedly, the primary outcome when treating these lesions is to prevent the development of pancreatic cancer. Accurate diagnosis and risk stratification in pancreatic cystic lesions are challenging as there is still a lack of consensus about the real impact of neoplastic pancreatic cysts on the development of pancreatic carcinoma. As a result, it is difficult to decide which treatment to recommend on a patient's basis. Treating pancreatic cysts is, in theory, a noninvasive option to reduce the risk of pancreatic cancer. Recently, multiple studies explored the feasibility of EUS-guided pancreatic cysts ablation. According to available data, the technique seems feasible, but the complication rate is not negligible and the patient selection in most of the studies is questionable. Unsurprisingly, many doubts have risen about the rational of cyst's ablation [34].

If we analyze the current literature, we find that a significant rate of lesions included in the published studies were totally benign, not requiring any type of treatment, like serous cystadenomas. This unclear patient's selection could lead to an overestimation of the benefits of the procedure and expose the patients to

unjustifiable risks. Another critical point is the definition of response, which, according to a recent expert agreement, is measured only by size reduction. Although some studies show a variation of genetic profile in the treated cysts, data are too scant to be considered evidence of total neoplastic epithelium ablation [29].

Moreover, local treatment, at best, eliminates the risk of developing pancreatic cancer in the epithelium of the ablated cyst. The rest of pancreatic parenchyma is still at risk, as we know that mucinous cysts like IPMN are often multifocal [35].

After all, we are in the very first phase of development in this field, and available studies can only show feasibility and initial promising results. We need more solid evidence that can be produced only by rigorous studies with strict protocols and precise designs. Last, but not least, we do not have valid information about costs.

With available data, we can only advise these procedures in selected patients and referral centers in the context of a strict study protocol and a previous multidisciplinary discussion of every single case. Patients should sign a specific consent, after receiving all the information about the risks and the possible benefits of the procedure. Information should point out the lack of evidence about the long-term efficacy of the procedure and the real impact on pancreatic cancer risk reduction.

In conclusion, there are still multiple points to be addressed, the most important ones regarding patient selection and costs in comparison to other strategies. The real goal remains the reduction of the incidence of pancreatic cancer in these patients; only follow-up will tell us the real impact of this treatment. It will be necessary to compare treated patients with matched groups using longer follow-up but, to obtain reliable data, future studies will have to select better the lesions to refer for treatment on a more specific protocol.

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Celiac Plexus Blockade/Neurolysis

16

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16.1 Introduction

Patients with chronic pancreatitis or pancreatic cancer often have significant pain that is difficult to control with traditional medications such as nonsteroidal anti-inflammatory agents (NSAIDs). Opioids are often used to help control the pain, but are commonly associated with side effects limiting their use. Therefore, celiac blockade/neurolysis has been used in these patients with the goal of improving pain control and quality of life while decreasing the risk of opioid-induced side effects.

The difference between celiac blockade and neurolysis lies in the injectate used—steroids are injected during blockade while typically a local anesthetic (bupivacaine or lidocaine) and a neurolytic agent (i.e., absolute alcohol or phenol) are injected during neurolysis. As injection of a neurolytic agent causes fibrosis which is thought to be permanent, celiac neurolysis (CN) is performed in patients with unresectable pancreatic cancer. In contrast, celiac blockade (CB) is performed in patients with non-life-threatening disorders such as chronic pancreatitis. This review will focus mostly on the use of CN in pancreatic cancer as the evidence exists for its use, while there is a lack of significant evidence on the use of CB in chronic pancreatitis.

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16.2 Relevant Anatomy

Understanding the relevant anatomy is necessary when performing CN/CB. Although the terms celiac plexus and splanchnic nerves are often used interchangeably, they actually represent different anatomical structures [1–3]. The splanchnic nerves are located cephalic to the diaphragm in a retrocrural position and anterior to the T12 vertebrae. The celiac plexus is located caudal to the diaphragm in an antecrural position, surrounds the origin of the celiac artery trunk, and comprises a dense network of ganglia and interconnecting fibers. Celiac ganglia vary in number [1–5], size (0.5–4.5 cm in diameter), and location (T12-L2 vertebra) [1]. The celiac plexus receives pain sensation from the neurons innervating the pancreas and most of the abdominal viscera (except for the left colon and pelvic organs) and transmits it to the thalamus and cortex of the brain where it is interpreted as pain [4, 5].

16.3 Technique

EUS-CB/CN is often performed in the outpatient setting under moderate or deep sedation. Prior to performing the procedure, it is important to review the patient's relevant allergies, medication use, and laboratory findings. In general, contraindications to performing CB/CN include (1) uncorrectable coagulopathy with an INR >1.5, (2) thrombocytopenia with platelets <50,000/L, (3) inadequate sedation, (4) altered anatomy (i.e., gastric bypass, extensive mass, or lymphadenopathy) that prohibits visualization or access to the celiac area, or (5) unable to obtain adequate consent. Informed consent is important to review the goals and adverse events of the procedure.

Patients are initially hydrated to 500–1000 mL of normal saline to minimize the risk of orthostatic hypotension following celiac injection. Continuous monitoring of the patient's vital signs is required throughout the procedure and for at least 2 h after the procedure. Prior to discharge, orthostatic vital signs should be checked to assess for orthostasis that may require additional fluid administration.

16.3.1 EUS-Guided Celiac Plexus Injection

Celiac plexus injection is the first described and most widely performed technique. This involves diffuse injection into the celiac plexus. Using the curvilinear echoendoscope, the aorta is visualized in a longitudinal plane from the posterior lesser curvature of the gastric fundus. The aorta is then traced distally to identify the celiac trunk, which is the first major arterial branch below the diaphragm. Using Doppler, vascular structures can be identified.

Typically, a 22-gauge needle is used for the injection. Although the types and volumes of injectate differ, we typically use a premixed solution containing 10 mL of 25% bupivacaine and 10 mL of absolute alcohol for neurolysis. The needle is primed with the injectate, advanced through the accessory channel, and affixed to the hub. The needle is then advanced under EUS guidance until the needle tip is placed approximately 5–10 mm away from the origin of the celiac trunk. Either the entire injectate volume can be inserted in the midline position (unilateral approach) or half of the injectate can be inserted onto each side of the celiac takeoff (bilateral approach).

16.3.2 EUS-Guided Celiac Ganglia Injection

A ganglion is a collection of nerve cell bodies and glial cells that are interconnected via a dense network of neural rami and septae of connective tissue. Ganglia are typically located adjacent to the celiac artery and anterior to the aorta. On EUS, they are predominately oval or almond-shaped, hypoechoic echogenicity (dark), have irregular margins, and range from 2 to 20 mm in size. Central hyperechoic strands or foci are commonly present within the ganglia, and hypoechoic threads (presumably neural fibers) can extend from the ganglia. We have previously shown that EUS can detect celiac ganglia in up to 81% of patients and accurately distinguish it from celiac lymph nodes [6–9].

The technique for ganglia injection has not been standardized. Our approach is to insert the primed needle into the center of ganglia <1 cm in size in the needle plane axis or into the deepest point in ganglia larger than 1 cm. The needle is slowly withdrawn as the injection is being performed. Each identified ganglia can be injected separately. As typically only a few mL of injectate is inserted into the ganglia, the remaining injectate can be dispersed into the plexus as described above.

One study on human cadavers found that high volume injection (4 mL) into the ganglion caused a larger spread of the neurolytic including into areas with unidentified ganglia compared to low volume injection (1 mL) [10]. Although the authors recommend high volume CGN, this requires confirmation in randomized control studies that it causes better pain relief, quality of life, or survival in patients.

16.3.3 EUS-Guided Broad Plexus Injection

First described by Sakamoto et al. in 2010, the injectate is inserted adjacent and anterior to the lateral aspect of the aorta at the origin of the superior mesenteric artery (second major branch off the aorta below the diaphragm) [11]. A 25-gauge needle was used as the needle needs to be advanced deeper using this technique. The remainder of the technique is similar to the plexus injection described above.

16.4 Efficacy of EUS-Guided Celiac Neurolysis

16.4.1 Overall Efficacy

Celiac plexus neurolysis (CPN) was first described in 30 patients with intra-abdominal malignancies by Wiersema et al. in 1996 [12]. In this group of patients, 82–91% required less or the same amount of pain medications to control their pain and 79–88% of patients had persistent improvement in their pain scores. Since then, there have been many studies on EUS-CN with differing techniques and endpoints. The mean pain relief benefit of alcohol neurolysis is 103 days [13] and subsequent EUS-CN appears to have less of an overall effect [14].

There are two meta-analyses published on the efficacy of EUS-guided CN in patients with pancreatic cancer [15, 16]. Puli et al. included eight studies on CPN in pancreatic cancer patients and found pain relief in 80.12% (95% CI 74.47–85.22), while Kaufman et al. only included three studies and found pain relief in 72.54%. Similar rates of pain relief were reported in case series published after the meta-analyses [17–19].

One study observed that the 49% of patients who had a heart rate change of 15 beats per minute (bpm) for at least 30 s during alcohol injection had better adjusted scores for pain (60 vs. 73, $p = 0.042$), less nausea and/or vomiting (65 vs. 81, $p = 0.04$), less financial difficulties (41 vs. 57, $p = 0.02$), less weight loss (45 vs. 65, $p = 0.007$), and more satisfaction with body image (52 vs. 62, $p = 0.035$) compared to those that did not have the heart rate change [20]. However, there was no difference in post-procedural opioid use and survival between the two groups.

A more recent randomized control study looked at celiac plexus neurolysis vs opioid therapy alone in patients with pancreatic cancer and followed them for 4 weeks [21]. It did not find a difference in regard to quality of life, pain scores, or average opioid consumption between the two groups. Therefore, they suggested that CPN should not be performed routinely for all patients with cancer-related pain.

16.4.2 Plexus vs. Ganglia Injection

The feasibility and efficacy of CGN were initially reported by Levy et al. in 2008 with 16 of 17 pancreatic cancer patients experiencing partial pain relief after injection [22]. A randomized control trial was performed with 34 patients assigned to receive either CGN or CPN [23]. The complete response rate defined as pain ≤ 1 on a scale of 0–10 was significantly higher in the CGN group than the CPN group (50% vs. 18.2%, respectively, $p = 0.010$) as was the partial response rate defined as pain ≤ 3 (73.5% vs. 45.5%, respectively, $p = 0.026$). There was no statistically significant difference in adverse events or duration of pain relief between the two groups.

Despite the possible pain relief benefit of CGN, we have described shortened life expectancy in patients who underwent CGN [24, 25]. In one study that compared patients who underwent any form of CN (EUS, percutaneous, surgical) to matched controls, patients who underwent EUS-guided CPN had a longer survival duration

than those who underwent EUS-CGN (200 days vs. 154 days, respectively, $p = 0.03$) [24]. This was also shown in a randomized double-blind trial that compared 60 patients who underwent CPN to 50 patients who underwent CGN in the setting of unresectable pancreatic cancer [25]. Pain response rates, quality of life, and adverse events were similar between the two groups. However, the median survival time was significantly shorter for those that received CGN (5.59 months) compare to those that underwent CPN (10.46 months, HR for CGN 1.49, 95% CI 1.02–2.19).

A clinical practice guideline composed by a group of expert endosonographers advised that EUS-guided CGN is not necessary [26].

16.4.3 Plexus vs. Broad Plexus Neurolysis

In a retrospective analysis of 112 patients at the single institution that reported the broad plexus neurolysis (BPN) technique, it was found that EUS-BPN in combination with EUS-CGN was significantly associated with pain relief [27]. The theory is that there is a wider distribution of spread of the neurolytic agent using the BPN technique. This is limited by its use in only a single institution and further studies need to be performed on this technique.

16.4.4 Bilateral vs. Unilateral Injection

A recent meta-analysis compared bilateral and unilateral CPN for pancreatic cancer [28]. Six studies, including three randomized control trials, were included in the analysis for a total of 437 patients. There was no significant difference in short-term pain relief [SMD 0.31 (95% CI −0.20 to 0.81)] or treatment response [RR 0.99 (95% CI 0.77–1.41)] between the two groups. Only one included study assessed either quality of life [29] or survival [30], which was similar between the two groups. However, the bilateral approach was associated with a statistically significant reduction in postoperative analgesic use [RR 0.66 (95% CI 0.47–0.94)] compared to the unilateral approach [28]. In contrast, a prior meta-analysis found that bilateral injection had higher rates of pain relief (84.54%, 95% CI 72.15–93.77%) compared to unilateral injection (45.99%, 95% CI 37.33–54.78%) [15]. This earlier meta-analysis combined both celiac neurolysis and blockade, likely accounting for some of the difference in the findings. The clinical practice guideline on EUS-CPN suggested the use of bilateral injection, but did mention that central injection is an acceptable option [26].

16.4.5 Volume of Injectate

One pilot study compared the use of 20 and 10 mL during EUS-guided CPN [31]. There was no difference in pain relief, duration of pain relief, and adverse events between the two groups. The authors concluded that using 20 mL of alcohol is safe.

16.4.6 Early Neurolysis

One randomized control trial studied the use of early EUS-guided CPN [32]. After EUS fine-needle aspiration (FNA) confirmed the presence of unresectable pancreatic adenocarcinoma, the group randomized 48 patients into either receiving EUS-CPN in the same session or conventional pain management. Pain relief was found to be greater in the early CPN group at 1 month [difference in mean percent change in pain score = −28.9 (95% CI −67.0 to 2.8)] and 3 months [difference in mean percent change in pain score = −60.7 (95% CI −86.6 to −25.5)]. When taking into account patients who did not receive chemotherapy or radiation (which may also improve pain), there were greater differences between the two groups. There was no difference in morphine consumption at 1 month (there was a trend for lower consumption at 3 months in the CPN group), quality of life, or survival between the two groups. Therefore, it is suggested that early EUS-CPN can be performed in patients with painful unresectable pancreatic cancer during the time of diagnosis [26].

16.5 Efficacy of EUS-Guided Celiac Blockade

Celiac plexus blockade (CPB) involves the injection of a local anesthetic (i.e., bupivacaine, lidocaine) with or without steroids (i.e., triamcinolone) into the celiac plexus. This procedure is typically performed in patients with chronic pancreatitis. Of the two meta-analyses described above, only Kaufman et al. did not include studies that injected a neurolytic agent in the setting of chronic pancreatitis [16]. In the six included studies, EUS-CPB was only 51.46% effective in managing abdominal pain in patients with chronic pancreatitis. This relief is thought to be temporary and only lasts a few weeks to months. Therefore, it is not typically performed as a primary form of pain management in these patients. The American College of Gastroenterology recently suggested to consider CPB for treatment of chronic pancreatitis pain [33]. However, they did mention that numerous studies did not show significant benefit of CPB in chronic pancreatitis.

Similar to CPB, the use of EUS-guided CPN for chronic pancreatitis is not recommended [26]. With the lack of efficacy and significant adverse events reported in the literature following EUS-guided CPN in this patient population (see the next section), the use of a neurolytic agent should be avoided in chronic pancreatitis.

16.6 Adverse Events of Celiac Blockade/Neurolysis

In a systematic review of complications in interventional endosonography, adverse events occurred in 21% of 661 EUS-guided CPN [34]. Majority of the adverse events were minor and self-limited lasting up to 48 h including transient diarrhea and orthostatic hypotension thought to be related to blockage of the sympathetic efferent nerves. All of the minor complications responded to intravenous fluid administration. Transient pain lasting up to 48 h occurred in 2% of EUS-guided

CPB and 4% of EUS-guided CPN cases. These patients were treated with a transient increase in the pain medication dosage and rarely hospitalization for pain control.

Major complications only occurred in 0.6% of EUS-guided CPB and 0.2% of EUS-guided CPN. Infectious complications with retroperitoneal abscess formation occurring after EUS-guided CPB have been described [35–37]. These patients were treated with drainage and intravenous antibiotics. One patient was diagnosed with a *Cladosporium macrocarpum* and *Streptococcus constellatus* brain abscess 3 weeks after EUS-guided CPN for chronic pancreatitis [38]. The authors thought that the microorganisms reached the brain through blood vessels through direct spread from the upper gastrointestinal tract during injection. The patient also had lymphocytopenia, which was thought to promote hematogenous spread.

Ischemic complications may occur secondary to the neurolytic agent causing arterial vasospasm, the destructive effect of the agent itself, or arterial embolization of the injectate. Three case reports describe ischemic events when EUS-guided CPN was used in patients with chronic pancreatitis [39–41]. One patient had ischemia of the pancreas, spleen, and gastric antrum following EUS-guided CPN [39]. Due to the extensive gastric necrosis, the patient eventually required a subtotal gastrectomy and Roux-en-Y gastrojejunostomy. Another patient who received EUS-guided CPN died after developing liver, kidney, and splenic infarction secondary to complete thrombosis of the celiac take off [40]. The third patient underwent 13 prior EUS-guided CPN over a 4 year period [41]. The last one was complicated by extensive gastric necrosis with perforation and a 5 cm profusely bleeding necrotic area of the aorta just above the celiac trunk, from which the patient eventually exsanguinated. Although all these reports focus on patients with chronic pancreatitis, one may presume that ischemic complications may also occur if performed for pancreatic cancer.

Three cases on permanent lower extremity paralysis have been reported after EUS-guided CPN [42–44]. Neurologic complications are thought to develop secondary to ischemia or direct injury to the spinal cord or somatic nerves. Spinal cord ischemia can result from thrombosis or spasm of the artery of Adamkiewicz, which is located to the left of the spine between T8 and L4 and perfuses the lower two-thirds of the spinal cord [45, 46]. Another neurological complication occurred in a patient who developed acute respiratory failure secondary to bilateral diaphragm paralysis after EUS-guided CPN [47]. This was thought to be secondary to cranial spread of the neurolytic agent to the phrenic nerves that innervate the diaphragm from below.

16.7 Conclusion

EUS-guided CPN is helpful in temporarily reducing pain in patients with refractory pain secondary to unresectable pancreatic cancer or in those that develop side effects of opioid medications. Interestingly, CPN has not been shown to affect quality of life or survival in this patient population. Early CPN at the time of EUS FNA cytological diagnosis may be the optimal time to perform this procedure. However, more information is needed on the technique such as the volume, type, and location

of the optimal injection. Although the evidence for the use of EUS-guided CPN exists in the setting of unresectable pancreatic cancer, it must be emphasized that both CPN and CPB is not recommended for the routine treatment of chronic pancreatitis particularly with the adverse event profile in this setting. Future considerations include the combination of EUS-guided CPN and tumor ablation during the same procedure or EUS celiac ganglion radiofrequency ablation, of which there are some pilot studies [48–50].

Disclosures None.

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Interventional Endoscopic Ultrasound in Patients on Antithrombotic Therapy

17

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17.1 Introduction

Interventional endoscopic ultrasound (EUS) includes endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), EUS-guided fine-needle biopsy (EUS-FNB), celiac plexus blockade/neurolysis (CPB), pancreatic fluid collection drainage, EUS-PD (pancreatic duct) drainage, EUS-guided biliary drainage, and endoscopic ultrasound-guided gallbladder drainage (EUS-GBD). EUS-FNA is the most common EUS intervention, is a reliable method for the diagnosis of many lesions of the gastrointestinal tract and peri-intestinal organs such as the pancreas, and is classified as a high-risk procedure in the international guidelines for the management of antithrombotic therapy (ATT) in endoscopic procedures. Bleeding is one of the adverse events associated with interventional endoscopic ultrasound, particularly in patients on ATT, and discontinuation of these agents before the endoscopic procedures is associated with an increase in thromboembolic events. A retrospective study of 2197 cases of ischemic stroke reported that stroke occurred in 114 patients (5.2%) who had interrupted therapy with warfarin or antiplatelet agents in the previous 60 days [1].

17.2 Risk of Bleeding in Patients on Antithrombotic Therapy: A Review of the Literature

The incidence of bleeding after EUS-FNA has been analyzed in a meta-analysis that included 10,941 patients, and the rate of bleeding complications after EUS-FNA was 0.13% [2].

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The bleeding occurrence rate in various studies has been reported to be 0–4%, [2–4] and severe bleeding is a rare event [5, 6].

Antithrombotic drugs increase bleeding risk during endoscopic procedures, and risk of thromboembolic events increases after discontinuation. There are few studies on the association between antithrombotic agents and EUS-FNA.

One prospective study comparing bleeding risk during EUS-FNA and/or Trucut biopsy (TCB) in 214 patients (241 lesions) taking aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) found that bleeding occurred in none (0 of 26) of the patients taking aspirin/NSAIDS, 33.3% (2 of 6) and 3.7% (7 of 190) of the patients in the LMWH, and control groups, respectively [7].

A recent retrospective study included 742 patients who underwent EUS-FNA for solid lesions; 130 of those patients were receiving ATT (ASA, cilostazol, thienopyridine, warfarin). Patients were divided in four subgroups: nonadministration, discontinuation of agents, continuation of aspirin, and heparin replacement. Overall bleeding rate was 0.9% (7/742) and all the events were intraoperative, and there were no severe bleeding events in patients on ATT. In the subgroups analysis, the rates of bleeding were 1.0% (6/611), 0% (0/62), 1.6% (1/61), and 0% (0/8) in the nonadministration, discontinuation of agents, continuation of aspirin or cilostazol, and heparin replacement groups, respectively. The rate of bleeding was very low in patients on ATT, and no thromboembolic event were observed [8].

Both the aforementioned studies concluded that the incidence of EUS-FNA-related bleeding is low, and aspirin administration may be continued during the procedure.

Kawakubo et al. conducted a prospective study on 2629 patients who underwent EUS-FNA, of whom 85 were receiving ATT; They analyzed the rate of bleeding and of thromboembolic events within 2 weeks after EUS-FNA. Bleeding after EUS-FNA occurred in 2 of 85 patients in spite of discontinuation of warfarin and dual antiplatelet therapy (2.4%; 95% CI, 0.6–8.3%). No thromboembolic events occurred.

The authors concluded that the rate of bleeding after EUS-FNA in patients taking antithrombotic agents might be considerable. In this study, there were no bleeding events in any of the patients who took aspirin or cilostazol without discontinuation. Therefore, use of EUS-FNA may be feasible with continued aspirin or cilostazol [9].

A single-center retrospective study included 908 patients undergoing EUS-FNA for pancreatic and non-pancreatic (lymph node lesions, hepatobiliary tract lesions, and lesions of the non-gastrointestinal tract) lesions. One hundred fourteen patients were on antithrombotic drugs (ASA, clopidogrel, cilostazol, dipyridamole, ticlopidine, warfarin, another antiplatelet agent, or DOACs). They observed six cases of significant bleeding (0.7%), four in the antithrombotic group (0.4%) and two (0.2%) in the non-antithrombotic group (odds ratio, 9.59; 95% confidence interval, 2.12–43.1; $P = 0.006$). The four cases of bleeding (3.4%, 4/114) in the antithrombotic group occurred in the continuation (3.2%, 2/63), discontinuation(2.4%, 1/41), and heparin subgroups (10%, 1/10).

The authors concluded for a slight increase in risk of bleeding, above all postoperative, in patients on ATT. There were no cases of severe bleeding. They concluded that EUS-FNA is a safe procedure for patients on antithrombotic therapy [10].

To clarify the feasibility of the other aforementioned techniques in patients on antithrombotic therapy, further studies are needed especially randomized controlled prospective trials.

A recent study on 12 patients on ATT with acute cholecystitis who underwent an endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) concluded that EUS-GBD might be a good option for these patients. Eleven (91.6%) of 12 patients underwent EUS-GBD with continuation of ATT, and 5 patients (41.7%) were receiving one or more antithrombotic drug. The rate of bleeding complications was 0%, and the technical success rate was 100% [11].

17.3 Management of Antithrombotic Agents

The management of antithrombotic drugs depends on the type of molecule, the procedure-related bleeding risk, and the thrombotic risk deriving from cardiovascular disease.

American Society of Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy/British Society of Gastroenterology (ESGE/BSG), and Asian Pacific Association of Gastroenterology/Asian Pacific Society for Digestive Endoscopy (APAGE/APSDE) guidelines provide recommendations on the management of antithrombotic therapy in the periendoscopic period.

Current guidelines classify EUS-FNA as a high-risk procedure. We can consider other procedures of interventional EUS as high risk [12–14].

The guidelines recommend continuing the aspirin/NSAIDs in the periendoscopic period.

With regard to thienopyridine (clopidogrel, prasugrel, ticagrelor) and dual antiplatelet agents (APA) therapy, ESGE/BSG and ASGE guidelines recommend considering cardiovascular risk. In case of low cardiovascular risk (CVR), stop thienopyridine 5 days before endoscopy; if high CVR, ASGE recommends discontinuing thienopyridine at least 5 days before the procedure or switch to ASA, while ESGE/BSG recommends liaising with a cardiologist about the risk/benefit of discontinuing APA and suggests discontinuation of drugs 5 days before the procedure only more than 12 months after insertion of drug-eluting coronary stent and more than 1 month after insertion of bare metal coronary stent.

APAGE/APSDE recommends discontinuing thienopyridine 5 days before endoscopy in case of high-risk procedure regardless of the CVR.

In case of dual APA therapy, all the international guidelines agree to withhold the thienopyridine and continue aspirin.

After the procedure, ASGE suggests to resume APA once hemostasis has been achieved, and a loading dose of drug should be considered among patients at risk for thrombosis.

Thienopyridine should be resumed up to 48 h depending on the perceived bleeding and thrombotic risks as suggested by ESGE/BSG guidelines; APAGE/APSDE recommends resumption once adequate hemostasis has been achieved.

For patients on warfarin undergoing high-risk endoscopic procedure as EUS-FNA, all international guidelines consider CVR: in case of low CVR, stop warfarin 5 days before endoscopy and check INR before the procedure ad ensure values <1.5 (ESGE/BSG) or <2 (APAGE/APSDE); in case of high CVR, discontinue warfarin 5 days before the procedure and administer bridge therapy with low-molecular-weight heparin (LMWH). ESGE/BSG recommends withdrawing the last dose of LMWH more than 24 h before the procedure. All guidelines recommend restarting warfarin the same day/evening of the procedure with usual daily dose after hemostasis has been achieved. In case of high CVR, ESGE/BSG and APAGE/APSDE suggest continuing LMWH until therapeutic INR range has been achieved.

With regard to direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, all guidelines recommend discontinuation before high-risk endoscopic procedures considering the drug-specific interval. ESGE/BSG and APAGE/APSDE recommend taking the last dose ≥48 h before the procedure, for patients on dabigatran with creatinine clearance (CrCl) of 30–50 ml/min taking the last dose of drug 72 h before the procedure. ESGE/BSG guidelines suggest a delay of 24–48 h in restarting DOACs after a high-risk procedure depending on the bleeding risk associated with the procedure. APAGE/APSDE recommends early resumption of DOACs after adequate hemostasis has been achieved. ASGE guidelines suggest delayed resumption of DOACs until adequate hemostasis is ensured. If therapeutic dose cannot be restarted within 12–24 h after the endoscopic procedure, thromboprophylaxis (LMWH bridge) should be considered to decrease the risk of thromboembolism.

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Sedation for Endoscopic Ultrasound

18

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18.1 Introduction

Endoscopic ultrasound (EUS) is uncomfortable and painful. Appropriate sedation is needed. Surveillance EUS such as follow-up for pancreatic cystic tumor is often repeated, so it is important to perform painless procedures for willingness to repeat the examination. The target sedation level in routine endoscopic examinations is moderate (conscious) sedation, where a patient retains the ability to purposefully respond to a verbal or tactile stimulus while cardiorespiratory function and airway protective reflex are maintained [1]. The following three points may increase the burden on the patient and provoke body movement; (1) when passing through the pharynx, (2) when passing through the pylorus, and (3) when shortening the duodenal second portion.

Gentle maneuver is needed, and additional sedation should be prepared.

Endoscopic ultrasound fine-needle aspiration (EUS-FNA) or therapeutic EUS using a puncture needle does not allow failure, and it requires stable level of sedation of long duration without body movement. Deeper sedation may lead to dangerous adverse events that require cardiopulmonary support, so it requires more careful administration of sedative agents. Before procedures, it is also critical to perform sufficient pre-evaluations for each patient. In this chapter, the sedation for EUS is reviewed.

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18.2 Benzodiazepine

Benzodiazepines have sedative, hypnotic (sleep-inducing), anxiolytic anticonvulsant, and muscle relaxant properties. Benzodiazepines enhance the effect of the neurotransmitter γ-aminobutyric acid (GABA) at the GABA-A receptor in the central nervous system. Midazolam, flunitrazepam, and diazepam are commonly used in the sedation for endoscopic procedures (Table 18.1). The disadvantages of diazepam are its strong venous irritation and the high frequency of phlebitis. Recently, midazolam and flunitrazepam are frequently used, because of a lower frequency of phlebitis and shorter half-lives [2].

Benzodiazepines may induce retrograde amnesia, and patients cannot often remember pain during the procedure. When patients show distress during the procedure, additional benzodiazepine may be administered in hope of this retrograde amnesia.

The dose of midazolam, flunitrazepam, and diazepam is shown in Table 18.2. Elderly patients should receive reduced doses of sedative agents, and a dose of half to two-thirds is enough. The reversal agent for benzodiazepine is flumazenil. Flumazenil can enhance patient recovery following endoscopic sedation. However, flumazenil has short elimination half-life (50 min), and there is a concern about the risk of re-sedation following its use.

18.3 Opioid Analgesics

Opioid analgesics mainly inhibit neurotransmission of pain by binding to specific opioid receptors that are present in the central nervous system and peripheral tissues. Opioid analgesics include narcotic analgesics and antagonistic analgesics. As

Table 18.1 Sedative agents and the characteristics

Agent	Classification	Characteristics	Half-life
Diazepam	Benzodiazepine	Long duration Phlebitis after injection	35 h
Midazolam	Benzodiazepine	Rapid onset Short duration	2–6 h
Flunitrazepam	Benzodiazepine	Rapid onset	20 h
Pethidine	Opioid agonist	1/5–1/10 as potent as morphine	4 h
Fentanyl	Opioid agonist	50–100 times more potent than morphine	3.6 h
Pentazocine	Opioid agonist-antagonist	1/2–1/4 as potent as morphine	2–3 h
Dexmedetomidine	α2 receptor agonist	Minimal respiratory depression Bradycardia/hypotension	2.5 h
Propofol	General anesthetic	Rapid induction, rapid recovery Pain upon injection	2–4 min

Table 18.2 Doses of sedative agents and reversal agents

Agent	Dose	Reversal agent
Diazepam	5–10 mg	Flumazenil
Midazolam	0.02–0.07 mg/kg	Flumazenil
Flunitrazepam	0.02–0.03 mg/kg	Flumazenil
Pethidine	35–70 mg	Naloxone
Fentanyl	1–3 μg/kg	Naloxone
Pentazocine	15–30 mg	Naloxone Doxapram
Dexmedetomidine	6 μg/kg/h (10 min) Followed by 0.2–0.7 μg/kg/h	Atipamezole (veterinary)
Propofol	0.5–1 mg/kg (induction) Followed by 2-6 mg/kg/h	–

narcotic analgesics, pethidine hydrochloride and fentanyl are most commonly used for endoscopic sedation. As antagonistic analgesics, pentazocine is also used. Opioid analgesics could reduce pharyngeal reflexes during scope insertion. On the other hand, opioid analgesics are associated with post-endoscopic nausea [3, 4]. Especially, the use of high-dose opiates in female patients might provoke nausea and vomiting after endoscopic procedures.

All opioids increase biliary tract pressure, but meperidine has a lesser effect [5].

18.4 α2 Adrenergic Receptor Agonist

Dexmedetomidine is a short-acting α2 adrenergic receptor agonist with anxiolytic, hypnotic, and analgesic effects. Clonidine is the first clinically used α2 adrenergic agonist. Clonidine was used as antihypertensive, and the unique side effect was hypnosis. Dexmedetomidine is ten times more selective towards α2 adrenergic receptor than clonidine. Locus coeruleus of the brain stem is the principal site for the sedative action and spinal cord is the principal site for the analgesic action, both acting through α2 adrenergic receptor [6]. Unlike GABA agonists such as midazolam, dexmedetomidine, which has a new mechanism of action, it is characterized by minimal respiratory depression. On the other hand, hypotension and bradycardia stand out (Table 18.1).

Dexmedetomidine is administered at an administration rate of 6 μg/kg/h for 10 min followed by a maintenance administration in the range of 0.2–0.7 μg/kg/h (Table 18.2). The combination of initial loading and maintenance administration is required, and the administration method is somewhat complicated. A 10-min timer is recommended so you do not forget to switch after 10 min. A recent meta-analysis of randomized controlled trials has showed that dexmedetomidine has a better sedative effect than midazolam in gastrointestinal endoscopy, especially in endoscopic treatment [7]. These benefits are achieved without an increase of cardiopulmonary complications. However, midazolam costs $1.25 per ampule, whereas

dexmedetomidine costs $44.4 per 50 ml syringe kit, which is considerably expensive. EUS-FNA or therapeutic EUS requires delicate endoscopic maneuver, relatively long treatment time, and more stable sedation state. Despite the high cost, dexmedetomidine is considered a useful option in EUS.

18.5 Propofol

Propofol (2,6-diisopropofol) is a sedative-hypnotic drug with an amnestic effect. Its hypnotic effect results from potentiating GABA through the $GABA_A$ receptor in a manner similar to that of benzodiazepines. It is highly lipophilic, and thus can rapidly cross the blood–brain barrier, resulting in an early onset of action [8]. Propofol is a short-acting agent with rapid metabolism, which has a short recovery profile regardless of the depth or length of the sedation period [9]. Rapid recovery has a major impact on patient satisfaction, post-procedure education, and endoscopy unit flow [10]. However, propofol has a narrow therapeutic window that can result in rapid depression of consciousness and cardiovascular functions (Table 18.1).

An initial bolus of propofol (0.5–1 mg/kg) is administered intravenously, followed by a continuous propofol infusion (2–6 mg/kg/h, with additional bolus administered as needed) or repeated bolus (10–20 mg) according to patient condition [11] (Table 18.2).

According to recent meta-analyses, propofol showed more effective and faster recovery time on endoscopy compared to benzodiazepine sedatives without increasing respiratory circulatory complications [12–14]. Another meta-analysis of randomized controlled trials comparing propofol and dexmedetomidine showed that propofol significantly increased patient satisfaction with gastrointestinal endoscopy [11]. The meta-analysis implies that propofol is expected to become an essential sedative agent for endoscopic examination. However, the manufacturers of propofol restrict its use solely to personnel trained in general anesthesia and that the United States Food and Drug Administration denied a petition by gastroenterologists seeking the removal of this particular restriction [15]. Sedation by non-anesthetists needs adequate training and certification for the non-anesthesia providers.

18.6 Combination of Sedative Agents

Benzodiazepine is often coadministered with opioid analgesics. Midazolam has rapid effect, so it is used as rescue agent for dexmedetomidine-based sedation. Additional doses should be carefully considered based on the monitoring and direct observation of the patient's condition.

Dexmedetomidine has relatively weak hypnotic effect. Dexmedetomidine is often coadministered with benzodiazepine and/or opioid analgesics. When hypotension or bradycardia occurs, the dose of dexmedetomidine should be decreased at first. When hypoxia occurs, additional doses of benzodiazepine should be discontinued, and dexmedetomidine is mainly used.

Propofol has minimal analgesic effect, so opioid analgesics are sometimes used as rescue agent for propofol-based sedation. However, recovery time from the combination of propofol and opioid analgesics might be longer than recovery from propofol only.

When hypertension occurs during endoscopic procedures, patients may feel pain. The checkpoints are abdominal distention due to perforation, and whether the body position causes straining any part of the body. Then, the administration of opioid analgesics is considered. When sever hypertension (>180 mmHg) is continuing after rescue by opioid analgesics, nicardipine is also considered.

18.7 Conclusion

In developed countries, it is expected that patients will demand more potent forms of sedation in the future. There is a saying from Japanese business philosophy called "triple win" [16]. "Triple win" means that business must promote the benefit of the seller, the buyer, and society as a whole. Endoscopic sedation should be also considered efficacy and safety for patients, burden and satisfaction for medical staffs, and financial and medicolegal factors for society. It is required to pursue "triple win" in endoscopic practice.

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Quality Measures in Endoscopic Ultrasound

19

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19.1 Introduction

Endoscopic ultrasound (EUS) is the only endoscopic procedure that offers the ability to access the so-called third space and diagnose lesions of the gastrointestinal (GI) tract and the mediastinum, which are out of the direct vision of the endoscope. It is therefore a well-established procedure that allows the endoscopist to accurately perform the preoperative staging and restaging of GI tumors, especially in the esophagus and rectum. Moreover, with the advent of EUS-FNA, EUS moved from a mere diagnostic procedure to an interventional one, allowing tissue sampling (e.g., from pancreatic lesions), which is not possible with any other diagnostic module, such as computed tomography (CT) or magnetic resonance (MR) [1].

Quality, on the other hand, has recently evolved to a basic parameter of GI endoscopy (GIE); its focus is to improve endoscopic practice, based on the available evidence, providing patients with the best clinical care [2], or as it has been stated by the Department of Health and Human Services Institute of Medicine (USA), quality represents "the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [3]. The need for quality initially arose in the early 2000s, as a result of reports of missed neoplastic lesions during GIE [3], but since then has evolved to a general demand affecting all implicated parties: patients, physicians and the healthcare system. Patients naturally focus on the quality of the offered

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service regardless of cost, physicians strive always for the best possible management, including avoidance of mistakes and complications, and the healthcare system asks for an internal quality system to ensure the quality of the offered services. In 2006, the American Society of Gastrointestinal Endoscopy (ASGE) published the first guidelines on quality measures in GIE, and in 2015, the first update was also released [4]. On the other hand, the European Society of Gastrointestinal Endoscopy (ESGE) has also addressed quality in GIE including EUS. In a recent publication, the "ESGE Quality Improvement Initiative" has highlighted various measures necessary in order to improve quality, when performing EUS and ERCP [5].

In general, quality is a qualitative parameter and therefore cannot be objectively rated. We need surrogate indicators or tools in order to achieve an accurate assessment of any measures we take, in order to improve GIE and EUS specifically. Quality indicators (QIs) are tools that we use to quantify the measures we undertake to provide quality in a given service. Specifically, for GIE, QIs are parameters that we use to assess the effectiveness of quality measures we implement during the procedure or, as it has been stated, to compare "performance of an individual or a group with an ideal or benchmark" [6, 7]; Qis, regardless of the specific endoscopic procedure, can reflect structural aspects of an endoscopy unit (e.g., availability of an examination), procedural aspects (e.g., diagnostic accuracy of a given procedure), or outcomes (e.g., an adverse event after the procedure) [8]. On the other hand, they can easily be subdivided according to the three phases of the procedure: before endoscopy, during endoscopy, and after endoscopy. This division helps us follow the various aspects that quality measures we apply in EUS might affect. Equally important, seeing these measures and their respective QIs under the spectrum of the aforementioned division (i.e., pre-, during and post-endoscopy) can help facilitate their critical appraisal, which is one of the main scopes of this review.

19.2 Before Endoscopy

Every interaction that takes place between the physician and the patient before the endoscopic procedure belongs to the pre-procedure time. Quality measures in this phase include the following:

- Indications for EUS:

  Patients must be clearly informed about the indications for the procedure and the availability of other diagnostic modules. At least 80% of all EUS procedures that are performed in a given endoscopic unit, or by a specific individual, should be made for an indication that is included in a published standard list of appropriate indications; moreover, this indication should be documented [8]. On the other hand, it should be noted that this does not exclude the possibility to perform EUS for an indication that is not listed in the guidelines. However, in such a case, the rationale should be clearly explained to the patient and should also be stated in the final report [9, 10]. For example, an obvious reason for preforming (or otherwise, for not performing) EUS outside the strict limits of "proper" indications is

local availability, which can determine the decision of the treating physician depending on available resources. For example, in cases of pancreatic head masses, EUS could be performed instead of magnetic resonance imaging (MRI) for assessment of vascular invasion according to local availability. Of course, and according to current guidelines, in such a case, if the lesion is deemed operable, there is no indication or need for EUS-FNA; in such a case, EUS should be used as a diagnostic/staging modality only [1, 2].

- Inform consent form:

  Patients and physicians should always have a thorough discussion about the EUS procedure (this applies ideally for all endoscopic procedures, regardless of its nature, of its diagnostic or interventional intent as well as its possible complications). All stages of the procedure, including benefits and—equally important—potential risks and possible complications of EUS and especially EUS-FNA, such as bleeding (0–0.5%), infection (<1%), and pancreatitis (0–2%), should be outlined with detail, according to the patient's capability to comprehend the meaning of the provided information [11, 12]. Low, but not negligible, rates of tumor seeding [13–19] and perforation [20–22] should also be mentioned. The patient must understand all information related to the procedure, have ample time to solve any queries, and subsequently sign the inform consent form (ICF); enough time should also be scheduled in order to provide patients with the possibility to withdraw their consent in case they wish to do so. The ICF should be signed in at least in 98% of cases [8]. If specific EUS techniques are going to be undertaken, e.g., celiac plexus neurolysis or radiofrequency tumor ablation, an additional explanation of specific complications linked to the intervention should also take place [2]. Another QI, related to the procedure, is the level of expertise of the endoscopist. In these days, patients are entitled to the right to know the level of expertise of the performing endoscopist, including their personal rates of complications [8].
- Management of medications:

  A full medical history should always be completed, focusing on use of anticoagulants and antiplatelet medication. In such a case, the type and dosage of the specific drugs being used must be documented, and changes made timely, before the procedure. Management of anticoagulants is based on a stratification of the risk of bleeding due to the endoscopic procedure versus the risk of complications due to the underlying cardiovascular disease. Endoscopic procedures are subdivided into low and high-risk. EUS is considered a low-risk procedure, whereas EUS-FNA is considered high-risk. In cases of simple EUS, anticoagulants can be safely continued, whereas DOACs should be omitted only on the morning of the day of the procedure. In cases of warfarin use, INR ought to be checked before the procedure, and if it is within therapeutic range, then EUS can be performed. In cases of EUS-FNA, the severity of the underlying cardiovascular disease must be assessed and management of anticoagulation and antiplatelets modified accordingly. More specifically, clopidogrel and prasugrel must be discontinued for 5 days if the cardiovascular risk is low. If this risk is high, then forming a liaison with a cardiologist is mandatory. DOACs must be discontinued for 48 h

(or 72 h in elderly patients with Creatinine Clearance of 30–50 ml/min). Warfarin can be discontinued until INR returns to <1.5 in case of low cardiovascular risk, or be substituted by low-molecular-weight heparin in case of high cardiovascular risk [23].

Use of antibiotics, following puncture of cystic lesions, as prophylaxis for infection, has been widely suggested and performed. Although this prophylactic administration is a practice widely exercised, it has also been debated, as the actual risk of infection has been noticed to be very low (less than 1%) [24]. The American Society of Gastrointestinal Endoscopy suggests use of prophylactic antibiotics merely in cases of EUS-FNA of mediastinal and pancreatic cystic lesions, defining though that more data from prospective, randomized studies are needed [25].

19.3 During Endoscopy

The time frame of the "endoscopic period" is usually defined as the time span beginning from the administration of sedation until the removal of the endoscope from the patient [2]. EUS is usually performed for specific indications and targeted clinical questions. Most common indications for EUS are tissue sampling and tumor staging (especially for pancreatobiliary indications), as well as characterization of subepithelial masses [26]. Thus, the most relevant QIs, which correlate to relevant quality measures, during this time interval should include rate of successful lesion sampling, accurate staging of malignancies, and designation of all requested structures [8].

Tissue sampling is evaluated only by rates of successful lesion sampling. According to the literature, diagnostic rates for malignancy of at least 71% in the case of pancreatic adenocarcinoma [27, 28] and 87% for nodal involvement due to esophageal cancer are acceptable [29–31]. Therefore, the endoscopist's personal score should be as close as possible to the aforementioned values. This can be facilitated by ROSE (rapid on-site evaluation) of the samples by an in-room cytopathologist to be sure that the acquired specimen has adequate material, or—in case of unavailability of ROSE—by performing a minimum of punctures of the lesions in question (e.g., 5–7 needle passes in case of pancreatic adenocarcinoma) [9].

Regarding tumor staging, depth of invasion and presence of pathological lymph nodes must be recognized. In the documentation, use of the TNM staging system is mandatory, as EUS is the best modality to access the "T" and "N" parameters of this system, while simultaneously lacking sensitivity for distant metastases (i.e., the "M" parameter) [32–34].

The first QI refers to the percentage that relevant structures (those representing the target of each specific examination) are documented. Relevant structures must be recognized at least in 98% of the cases. In case of subepithelial masses, the layer from which the mass originates should always be recognized and documented with the help of appropriate images. Moreover, these images should clearly display the size and specific morphological features of the lesions/structures that are in question [8]. A pivotal role in any endoscopic procedure, EUS included, is an effective

sedation. Quality measures regarding sedation include documentation of the following parameters: vital signs during sedation, doses and route of administration of all administered medications, use of reversal agents, and interruption or premature termination of the EUS due to sedation-related issues [8].

19.4 After Endoscopy

Post-endoscopy time includes many important measures, which also contribute to the quality of an EUS procedure:

(a) recognition and proper management of possible adverse events,
(b) discussion with the patient and offering instructions for the immediate post-endoscopy time,
(c) management of medication and especially anticoagulants after the endoscopy,
(d) in-depth explanation of the findings, and
(e) follow-up of the histology/cytology.

Adverse events of EUS are relatively rare, especially if no EUS-FNA or EUS-guided biopsy is performed [12, 35]. However, in the rare case that they occur, the endoscopist should always be in a position to timely recognize any of them and—equally important—to be able to manage them appropriately. It has been said that "the worst complication in GIE is non-recognition or denial of a complication." This applies especially in cases of pancreatobiliary GIE, including EUS. Usually, complications such as bleeding and pancreatitis are mild and thus do not need any special interventions for their treatment; on the other hand, in the rare case of perforation, decisions must be taken quickly, in order to achieve an effective treatment [36, 37].

As for every endoscopy, patients must be informed by the performing endoscopist about the findings of the procedure they underwent, as well about the impact these findings might have on their further management. Although, this measure seems obvious and should apply for every procedure, this is not always the case. The latter has been attributed to various reasons, including organization factors, especially in large referral centers with a large workload, where there is "no time to explain" the findings to the patient, but also sometimes even the healthcare system is organized in such a manner that it may be the culprit; For example, in many systems, patients are referred for GIE from general practitioners, who then are the ones with the duty to inform the patient, a task not always easy to be performed by a nonspecialist, especially when talking about complex and specialized procedures, as is the case for EUS. Moreover, timely information of the patient on the cytopathology or histological results has been deemed as a valued QI on behalf of patients and has been reported to be even more important than a good long-term relationship with the endoscopist [38]. Experience has shown that in many cases even this measure can also be rather problematic.

Providing the patient with some basic post-procedural information, including adequate advice to avoid driving and intense physical activity, is mandatory, as

negligence to do so, may result in dangerous consequences for the patient. Medications can be restarted in case of EUS or EUS-FNA after the endoscopy. Only in cases of suspected bleeding, case-by-case management is advised [39, 40].

The endoscopist is in charge of receiving the pathology/cytology results and interpret them. As discussed above, EUS is usually performed in order to answer a specific clinical question. Given the relatively low-negative predictive value of EUS-FNA for differential diagnosis of pancreatic cancer from chronic pancreatitis with a pseudotumoral mass, which reached a mere 73.9% in a recent publication [41], the endoscopist is assigned to interpret the findings and to decide whether a repeated EUS or performing other diagnostic modalities is the proper management for the specific patient. As far as repeating the procedure is an option, one could attempt EUS-guided core biopsy which seems to be an attractive alternative (e.g., in the aforementioned study its negative predictive value reached 87%). It should be pointed out here that cooperation with the cytopathologist/pathologist, as well as other medical specialists implicated each and every specific case (especially radiologists, internists, or surgeons), may contribute to improvement of the clinical decision.

Finally, another QI that should be taken into account is the patient's satisfaction; this QI is also a vital one that occasionally is not regarded as an important factor by endoscopists, an attitude that should change, as the latter seems to incorporate more than just issues of sedation and post-procedural pain, but also reflects the impact of most of the quality measures undertaken throughout the whole procedure, as well as the general handling of the case by the responsible physician [42, 43].

In conclusion, in these paragraphs, a concise review of the definition and the need of quality in EUS was presented, followed by some of the most important quality measures that are used in everyday clinical practice. It is very important to keep in mind that these measures should not be regarded as a mere theoretical wish list but should be rather seen as points in a practical roadmap, meant to improve patients' outcomes and clinical care.

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Conclusive Remarks and New Perspectives

20

Antonio Facciorusso and Nicola Muscatiello

20.1 General Concepts

A pancreatic lesion, either solid or cystic, may be related to a wide spectrum of benign and malignant diseases; in this setting, it is of paramount importance to distinguish between malignant and benign tumors and to identify those patients who need to be referred to surgery.

Recent advancements in the field of endoscopic ultrasound (EUS) allow to reach a definitive diagnosis without the need of further examinations thus decreasing the cases of unnecessary surgery [1].

EUS plays a pivotal role also in the management of inflammatory pancreatic fluid collections (PFCs) that are associated with increased morbidity and mortality, especially in patients with necrotizing acute pancreatitis. The vast majority of PFCs do not require any interventions as they normally undergo spontaneous resolution with conservative management; however, when needed, EUS-guided drainage is advised to be the best choice for the majority of these patients [2].

In spite of the aforementioned concepts, EUS may sometimes not be sufficient for a correct diagnosis of a variety of pancreatic lesions. Nowadays many new diagnostic techniques have been developed in order to obtain enhanced pancreatic imaging; among these, contrast-enhanced endoscopic ultrasound and endoscopic ultrasound-elastography are of particular interest [3–5]. Contrast-enhanced endoscopic ultrasound combines the advantage of the study of the pancreas with a contrast agent with high-resolution ultrasonography of the organ whereas EUS elastography investigates tissue elasticity changes caused by inflammatory and neoplastic lesions. These new techniques, alone or in combination, increase diagnostic

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accuracy, sensitivity, and specificity of EUS in the detection and differential diagnosis of pancreatic lesions; furthermore, they can prove useful in guiding endoscopic ultrasound tissue acquisition [3, 5].

20.2 EUS-Guided Tissue Sampling

Since its introduction decades ago, EUS tissue acquisition (EUS-TA) has become the technique of choice for the diagnosis of solid pancreatic lesions. In the last years, we are experiencing a paradigm shift from simple cytological diagnosis with fine-needle aspiration (FNA) to histological diagnosis with fine-needle biopsy (FNB).

The development of EUS-FNB needles has generated a great deal of interest in the field primarily based on proposed advantages over EUS-FNA of improving diagnostic accuracy, improving procurement of samples with preserved tissue architecture and allowing for immunohistochemistry or special stains required for certain diagnoses, obviating rapid on-site cytologic evaluation (ROSE) and obtaining results in fewer passes, and thus potentially improving the efficiency and costs associated with EUS-TA [6].

In over past 2–3 years, there has been worldwide spread in the use of newer EUS-FNB needle designs, with end-cutting needles introduced in the endoscopic practice [7]; however, although these novel needle designs are thought to improve tissue capture and several studies have been published testing these novel devices [8], there is still limited evidence on their diagnostic performance in terms of diagnostic yield and histology core procurement [9, 10].

Recently, a through-the-needle biopsy (TTNB) microforceps device (Moray Microforceps®, US Endoscopy, Mentor, OH, USA) that can be passed through a standard 19-gauge EUS-FNA needle was developed for histologic sampling of pancreatic cystic lesions (PCLs). The main advantage of TTNB is to obtain adequate specimens retaining the stroma covered with the epithelial lining and, therefore, to preserve the histological architecture of the sampled tissue [11]. Several recent meta-analyses demonstrated the clear superiority of TTNB over standard FNA in PCLs [12, 13], although some safety concerns were recently raised in the clinical practice [14]. Furthermore, while antibiotic prophylaxis was found to be unnecessary in EUS-FNA of PCLs, it is still unclear whether this statement could be applied also to patients undergoing TTNB sampling [15, 16].

There is still limited evidence on the use of confocal laser endomicroscopy (CLE), one of the novel imaging technologies that allows microscopic visualization of the mucosal surface epithelium [17]. Although it seems that optical biopsy at real time may further improve the diagnostic yield by reducing the sampling error thus obviating to the need of ROSE [18], further studies are needed to prove its efficacy.

20.3 EUS-Guided Drainage of PFCs

Last decade has seen a paradigm shift in the management of PFCs, largely due to the rapid evolution of EUS from a diagnostic into a therapeutic modality. Rapidly evolving therapeutic indications and techniques were coupled by innovation in accessories like large caliber lumen apposing metal stents (LAMs); this has resulted in EUS-guided drainage of PFCs proving its effectiveness as a minimally invasive therapy with lower rate of complications as compared to other invasive approaches [19, 20].

Pancreatic pseudocysts usually improve after initial drainage, and LAMs can be removed simply by pulling with a rat-toothed forceps using a regular front-view gastroscope.

However, multiple questions in this field remain unanswered. It is unclear if up-front necrosectomy is better and safer than step-up necrosectomy; the role of adjunctive irrigation and drainage strategies is based on expert opinion only and should be rigorously investigated; prototypes of LAMs with an anti-reflux valve to facilitate one-way drainage of the collections and multigated drainage have yet to be evaluated in a comparative prospective fashion [21]. Finally, the long-term benefits and adverse events of LAMs beyond 5 years need to be assessed.

20.4 Therapeutic Role of EUS in Pancreatic Cancer Patients

The current standard of care for locally advanced pancreatic cancer is chemotherapy which provides patients with a median survival of 6–8 months. The addition of conventional external beam radiotherapy (EBRT) was previously associated with toxicity and is not routinely recommended; on the other hand, the development of stereotactic body radiotherapy (SBRT) potentially allows more selective delivery of radiation to the tumor. However, in order to deliver SBRT precisely, the placement of fiducial markers helps to compensate for tumor motion during respiration by tracking and accurately determining tumor boundaries. Although fiducials can be implanted percutaneously and laparoscopically, the minimally invasive EUS-guided approach has become the method of choice [22].

EUS-guided ablation, brachytherapy, and antitumor agent injection have been described to date [23–25]. EUS-guided brachytherapy and RFA have been shown to be feasible and safe procedures, and potentially offer local disease control [23]. Other potential techniques of EUS-guided treatment of pancreatic cancer are still considered experimental, with many of them appearing to be safe and reasonably well tolerated. However, their effectiveness and exact role in oncological treatment have yet to be established. Clinical trials with many of the techniques/agents described are underway, and multicentric randomized trials with prospective design are eagerly awaited.

Patients with pancreatic cancer often experience pain refractory to traditional medications such as nonsteroidal anti-inflammatory agents or opioids. EUS-guided celiac plexus neurolysis (CPN)/blockade has been advocated in the treatment algorithm for these patients with satisfactory results.

Early CPN at the time of EUS-FNA cytological diagnosis may be the optimal time to perform this procedure [26]. Although the evidence for the use of EUS-guided CPN exists in the setting of unresectable pancreatic cancer, it must be emphasized that it is not recommended for the routine treatment of chronic pancreatitis particularly with the adverse event profile in this setting. Future considerations include the combination of EUS-guided CPN and tumor ablation during the same procedure [27] or EUS celiac ganglion radiofrequency ablation [28].

20.5 New Perspectives

In conclusions, like many other fields of medicine, EUS is an evolving topic. The endoscopist should be aware of the main changes in this field, particularly with regard to newer diagnostic devices and interventional techniques.

EUS-guided celiac ganglia neurolysis, celiac plexus block, or radiofrequency ablation might represent a better option as compared to standard EUS-CPN in patients with pancreatic cancer. EUS-guided radiofrequency ablation may be used also as direct therapy against pancreatic cancer, whereas EUS-guided tattooing or fiducial markers placement already represent a standard for those unresectable patients suitable to SBRT.

Newer FNB devices are increasingly used in the clinical practice, and several ongoing trials will help to define their exact role in the field, in particular in cases specifically requiring histological diagnosis such as autoimmune pancreatitis.

Finally, EUS-guided drainage of PFCs plays a pivotal role in the management of these conditions, and preliminary studies shed light on new applications of LAMs in pancreatology.

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