Modern ultrasound imaging of pancreatic tumours

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Abstract
In patients with solid pancreatic lesions (SPL) the differential diagnosis has to be evaluated to determine the indications for radical surgery, pancreatic parenchyma saving strategies or follow-up. Contrast enhanced (endocopic) ultrasound and elastography facilitate further characterisation of SPL. The majority of cases with pancreatic ductal adenocarcinoma exhibits hypoenhancement with contrast-enhanced ultrasound. Elastographic soft SPL are benign with very few exceptions, whereas stiffer SPL can be malignant or benign. This article reviews the current use of modern ultrasound imaging techniques including contrast enhanced ultrasound and elastography for detection and characterization of solid pancreatic lesions. In particular, the unexcelled diagnostic potential of multiparametric endoscopic ultrasound to detect and characterize small solid pancreatic lesions is highlighted.

Key words
Ultrasound; endoscopic ultrasound; real-time; tissue elastography (TE), pancreas, neuroendocrine tumour

Abbreviations
NET

Introduction, the smaller the lesion the better the prognosis
Symptomatic pancreatic ductal adenocarcinoma (PDAC) is the most common diagnosed solid malignant tumour of the pancreas, which is generally diagnosed at a late stage with or without metastases [1,2]. Most internationally recognized guidelines [3-6] recommend radical surgery for all small solid pancreatic lesions (SPL) unless a strong suspicion of an etiology other than PDAC is suspected or contraindications are present. In earlier times preoperative diagnosis of PDAC < 20 mm (T1) was reported to be < 5 %; in a large series including 13.131 patients, only 3.1 % of cases were staged as stage T1a [1]. Very early
diagnosis in asymptomatic stages is crucial to improve prognosis [7-11]. Data from the surveillance, etiology and end results (SEER) program [12] as well as from the Japanese Pancreatic cancer registry [13] show that the smaller the lesion at time of diagnosis the longer the expected 5 year survival rate. In the SEER database (2000 – 2010) PDAC ≤ 20 mm account for only 14.8% of patients with pancreatic cancer, but for 28.2% of 5 year survivors [12]. The 5-year survival rate may reach up to 30 - 60 % in very small PDAC with curative radical surgery [9,14-17] compared to be < 5 % in general [https://seer.cancer.gov/]. Progress from early PDAC to T4-stage may occur in less than 1 year [1]. In today’s view a SPL diameter of ≥ 15 – 20 mm is about 80 % predictive of PDAC [7,18,19]. Neurendocrine neoplasia has a much better 5 year survival depending on the specific histology and hormone production [20,21].

The accuracy of traditional imaging methods, e.g ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) in the differential diagnosis of pancreatic masses was disappointing [6,16,22]. CT was the recommended technique for diagnosis and staging of pancreatic cancer [14,16,22-24] with unsatisfying results for the detection of small SPL < 20 mm [7,25,26]. CT does not reliably allow differential diagnosis of small SPL [9,27]. Endoscopic ultrasound (EUS) is considered to be the imaging method of choice to exclude PDAC [24,28,29]. Based on 22 studies including 1170 cases, the pooled sensitivity of EUS for the detection of SPL is 94% and markedly higher than described for multidetector CT, MRI and transabdominal US [30]. According to meta-analytic data, EUS has a diagnostic yield of 70% to detect a SPL in patients with indeterminate multidetector CT scan; in 42% PDAC finally was diagnosed [31]. Moreover, EUS offers the opportunity to detect asymptomatic PDAC [32]. A recent retrospective multicenter analysis of 200 small PDAC showed, that tumor diagnosis only in 52.6% of cases was possible due to direct visualization of the tumor by imaging techniques. In 74.8% of cases dilatation of the main pancreatic duct (MPD) was the clue to diagnosis. Sensitivity of EUS for tumor detection was 92.4%, whereas transcutaneous ultrasound (TUS), computed tomography (CT) and magnetic resonance imaging (MRI) had a sensitivity of only 67.3, 65.8, and 57.5%, respectively [33]. The high diagnostic value of MPD dilatation or stricture for diagnosis of small PDAC was highlighted also in other studies using TUS and EUS [34-36]. An unmatched diagnostic ability of EUS was also described for the detection of pancreatic neuroendocrine tumors (PNETs). A retrospective study showed that CT overlooked 68% of PNETs measuring < 10 mm, whereas
sensitivity of EUS was 100% [37]. According to a recent meta-analysis, EUS has an additional diagnostic yield of 28% over radiological imaging and up-to date scintigraphic techniques to detect PNETs [38]. Several studies have shown superiority of EUS in characterisation of SPL [25,39-43]. EUS is recommended by the National Comprehensive Cancer Network guidelines [14]. Contrast enhanced imaging techniques allow the improved characterisation before radical surgery and fine needle biopsy in many circumstances facilitates preoperative differential diagnosis [2,7]. EUS-guided tissue sampling is 85 - 92% sensitive and nearly 100% specific for the diagnosis of pancreatic malignancy [44-47]. However, a recent study showed, that sensitivity of EUS-FNA significantly decreased with decreasing mass size [48]. In conclusion, for the detection and characterisation of small SPL EUS is the imaging technique of choice.

**Contrast enhanced ultrasound (CEUS) and/or contrast enhanced endoscopic ultrasound (CE-EUS)**

The introduction of contrast enhanced endoscopic ultrasound (CE-EUS) has improved the performance of endoscopic imaging [49,50]. The pancreatic multicentre ultrasound study (PAMUS) with more than 1000 patients and other studies using contrast enhanced ultrasound (CEUS) and CE-EUS showed an improved diagnostic accuracy for characterization of focal pancreatic lesions [29,51-53]. Meta-analyses demonstrated a 90% accuracy of CEUS and CE-EUS to differentiate PDAC from other etiologies of SPL [54-57]. Recent data of 394 asymptomatic patients or patients with unspecific symptoms with incidentally found small solid SPL ≤ 15 mm and a definite histological or cytological diagnosis were retrospectively evaluated. Patients with significant weight loss, jaundice, or a history of chronic pancreatitis were excluded [32]. Furthermore, patients with defined hormone production, genetically determined diseases and cystic or semisolid lesions were excluded [21,58,59]. Patients with neuroendocrine neoplasia and hormone production were analysed as well and the results were published in a separate paper [21]. The first detecting imaging methods have been transabdominal ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT) or magnetic resonance imaging (MRI). The work up varied regarding the availability of imaging techniques, biopsy and surgery.

Only 146/394 small SPL (37 %) were finally diagnosed as PDAC. In the subgroup of SPL measuring exactly 15 mm (n= 83) 51 lesions proved to be PDAC (62 %). In contrast, only 95
of 311 SPL < 15mm (31 %) were diagnosed to be PDAC (p < 0.01) [32]. The most important differential diagnosis of PDAC is neuroendocrine tumour (NET). 156/394 small SPL (40 %) turned out to be typically hyperenhancing [51,52] neuroendocrine tumors (NET). 129/156 (83 %) NETs were benign and 27/156 (17 %) malignant [32]. The third most common etiology was pancreatic metastases (n= 28; 7 %). Other differential diagnoses included often hypervascular serous microcystic cystadenoma (SMCA), solid pseudopapillary tumor (SPT), non-Hodgkin lymphoma (NHL), focal pancreatitis, intrapancreatic accessory spleen, and hamartoma, and [28,29,51,52], whereas mucin filled intraductal papillary mucinous neoplasia (IPMN) and isolated necrosis are non-enhancing [32]. It can be concluded that the smaller the size of a SPL the less common the diagnosis of PDAC and the more frequent the diagnosis of NET and other rare etiologies.

Contrast enhanced ultrasound (CEUS) and/or contrast enhanced endoscopic ultrasound (CE-EUS) were performed in 219 of 394 patients using intravenous injection of 2.4 mL (CEUS) and 4.8 mL (CE-EUS) SonoVue® according to the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [28,60-63]. Iso-, hyper- or hypoenhancement in comparison to the surrounding pancreatic parenchyma was documented [32,64]. In 57 of 62 patients (92%) PDAC exhibited hypoenhancement, whereas in non PDAC patients 132 of 157 (84%) SPL showed iso- or hyperenhancement in comparison to the surrounding pancreatic parenchyma. In addition, 91 of 102 NET (89%) were hyper- or isoenhancing resulting in a correct differential diagnosis of PDAC and non PDAC in 189 of 219 patients (86%) [32]. The results using CEUS were better compared to CT; CT did not delineate a focal pancreatic lesion in 14 of 38 patients with complete reports of CE-EUS and CT (37%; PDAC, n = 6 and NET, n = 8; median diameter 8 mm (4 – 12 mm)) [32] and the ultrasound contrast agent SonoVue is strictly intravascular and therefore, highly sensitive [65]. These results are in concordance with the findings published in more than 1000 histological proven focal pancreatic lesions and earlier studies using contrast enhanced ultrasound techniques [29,49]. Eye catching features have been published for the imaging of serous microcystic neoplasia with only microscopically detectable cysts mimicking a solid lesion [66].

In conclusion and in accordance with the published literature CEUS and CE-EUS allow differential diagnosis of solid pancreatic tumours in about 90 % of cases. This knowledge has
been reflected in recent guidelines [60,61] and should be applied also due to cost effectiveness reasons [67].

**Endoscopic Ultrasound versus transcutaneous ultrasound**

In addition to the recently published results in small and solid pancreatic lesions using conventional and transcutaneous ultrasound (TUS) and endoscopic ultrasound (EUS) [32] we herewith report data on the comparative results of two techniques. TUS was performed prior to EUS in 45 patients (median age: 59 years; range: 18 - 81 years; 20 males and 25 females) with 25/45 malignant (56 %) and 20/45 benign (44 %) SPL. In 5/45 patients (11 %) the SPL was not detected by TUS prior and after EUS. In 6/45 patients (13 %) TUS detection of the lesion and CEUS were possible only with knowledge of the EUS finding. In 34/45 patients (76 %) the SPL was detected by TUS prior to the EUS examination and CEUS was performed as described. The CEUS results were concordant except in one patient with hyperenhancing lesion using EUS whereas the SPL was hypoenhancing by TUS. We conclude that most SPL can be detected by TUS, and CEUS evaluation is possible for further characterization [63] (Figure 1 and 2). The value of handheld devices using point of care has to be determined [68-72].

**Ultrasound elastography (USE)**

Ultrasound elastography (USE) allows tissue stiffness assessment by virtual palpation. Two main types of USE are used for the evaluation of the pancreas and of other organs [73-83]. Ultrasound based strain elastography (SE) using endoscopic ultrasound has been established for the assessment of small focal pancreatic lesions and the examination technique has been described in detail including the appropriate transducer, frequency selection, frame rate, line density, palpation speed and amplitude, noise filters, persistence, dynamic range of elasticity and other quality parameters (e.g., strain graph display) [80,81,84-87]. Soft small solid pancreatic lesions are typically benign, whereas stiffer (harder) SPL in otherwise healthy pancreatic parenchyma can be malignant or benign. Recently a study was performed with 218 patients with solid pancreatic lesions ≤ 15 mm and a definite histological diagnosis [88]. 50% of this particular group of small SPL turned out to be soft compared to the surrounding pancreatic parenchyma. It could be shown that especially in patients with small pancreatic lesions, EUS elastography can rule out malignancy with a high level of certainty if
the lesion is displayed as soft. In larger SPL > 30 mm the results are less convincing mainly due to the heterogeneity of the lesions but also by concomitant changes of the surrounding pancreatic parenchyma [88]. The examination technique has to follow certain rules, which have been described in detail [85,86]. Elastography is not able to decisively differentiate focal pancreatitis from PDAC since also chronic focal pancreatitis can be stiffer than the otherwise healthy pancreatic parenchyma. Strain elastography is also useful in diagnosing autoimmune pancreatitis since the entire organ shows stiffer tissue properties before B-mode changes are visible [89-93]. Circumscript pancreatic tuberculosis is also stiffer than the surrounding pancreatic parenchyma [94,95], whereas the application and correct interpretation of elastography in chronic pancreatitis is more difficult and semiquantitative strain exploiting elastographic techniques are preferred.

The current role of shear wave elastography has to be determined. Shear wave measurements are higher in PDAC with shear wave velocities > 3 m/s [96-99] compared to the surrounding pancreatic parenchyma.

**Conclusion**

In patients with SPL etiological differentiation is necessary to facilitate reasonable decisions on further management: radical surgery in patients with resectable PDAC, oncological treatment in patients with non-resectable malignancy, pancreatic parenchyma saving strategies or surveillance in benign neuroendocrine neoplasia or follow-up in small benign lesions [32] (Figure 3). Based on the enhancement pattern in CEUS and on elastography findings, further characterisation of SPL is possible. Hypovascularity is observed in approximately 90% of PDAC. Soft SPL are benign with very few exceptions, whereas stiffer (harder) SPL in otherwise healthy pancreatic parenchyma can be malignant or benign. Approximately 60% of small SPL ≤ 15 mm are diagnosed with etiologies other than PDAC [28,51,52]. In patients with hypervascular and/or soft SPL tissue acquisition is, therefore, recommended prior to treatment decisions as radical surgery might not be appropriate. Nevertheless, about 40 % of patients with small SPL revealed PDAC at a very early stage with better prognosis. Patients with hypovascular SPL ≤ 15 mm should be primarily and radically operated since this finding is indicative for PDAC. In patients with serous cystadenoma, mesenchymal lesions, intrapancreatic accessory spleen and non-functional NET < 10 mm and
a Ki67-index < 3%, follow up may be recommended whereas NET > 10 mms and Ki67-index of > 3 % will often be operated due to their malignant potential [100].

Figure Caption

Figure 1  Neuroendocrine neoplasia. Focal pancreatic lesions hyperenhancing with contrast enhanced imaging techniques (7 x 6 mm, between markers) using endoscopic ultrasound (a) and transcutaneous contrast enhanced ultrasound (b). The soft elastographic image is shown as well indicating a benign lesion (c). The handheld device Vscan did also demonstrate the lesion (d). A neuroendocrine neoplasia was diagnosed by biopsy and histopathological evaluation.

a

b

c
Figure 2  Neuroendocrine mixed solid-cystic neoplasia. Solid-cystic focal pancreatic lesion (marked with arrows) using B-mode (a) and hyperenhancing with contrast enhanced endoscopic ultrasound (b) and transcutaneous B-mode (c) and contrast enhanced ultrasound (d). A neuroendocrine neoplasia was diagnosed by biopsy and histopathological evaluation.
Figure 3  Diagnostic algorithm. Diagnostic algorithm in small pancreatic lesions (SPL) (with permission of Dietrich and Burmester) [50].
References


