Contrast-enhanced ultrasound of small focal solid pancreatic lesions: A must!

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INTRODUCTION OF CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND

The general use of contrast agents (if not contraindicated) is obvious and has never been questioned performing computed tomography (CT) and magnetic resonance imaging (MRI).[1,2] Why should this not be true for ultrasound to analyze vascularity and perfusion and thereby the etiology of pancreatic lesions? The introduction of ultrasound contrast agents has strengthened the value of ultrasound.[3-6] In 2003, contrast-enhanced endoscopic ultrasound (CE-EUS) was introduced for the first time.[7,8] CE-EUS combines the advantage of high-resolution ultrasound of internal organs with the administration of ultrasound contrast agents.[7,9] In the following years, CE-EUS has been mainly established in the differential diagnosis of solid and cystic pancreatic lesions,[5,9-18] epithelial and submucosal tumors of the gastrointestinal tract,[19,20] lymph nodes,[21-25] and less common applications including the biliary tract[26] and vascular indications.[27-29] As has been shown in several studies including a recently published multicenter trial with more than 1000 patients (Pancreatic Multicenter Ultrasound Study), CE-US and CE-EUS improve the diagnostic accuracy of ultrasound techniques for characterization of focal pancreatic lesions.[30-34]

EARLY DETECTION OF SMALL SOLID PANCREATIC LESIONS (SPLs)

Preoperative diagnosis of T1 carcinoma (<20 mm) is important for improved survival.[35] Independently of etiology, most small SPLs are detected incidentally in asymptomatic patients.[36] In large cohorts of SPL, lesions other than pancreatic ductal adenocarcinoma (PDAC) have rarely been reported (5%–11%).[37,38] In most patients (up to 95%), PDAC is diagnosed late with locally advanced or metastatic disease[39,40] with a low overall 5-year survival rate <5%.[41,42] Due to the fact that the prevalence of both pancreatic neuroendocrine tumors and metastases is reported to be only approximately 3%, most guidelines do not recommend to exclude other pathologies than PDAC before surgery.[34]

EUS is the method of choice to exclude pancreatic neoplasia and to detect and characterize small

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SPL.[6,30,31,33,34,43-46] Several studies have shown superiority of EUS in detection and characterization of PDAC.[34,47-52] This has been strengthened by the inclusion of EUS in the National Comprehensive Cancer Network guidelines.[53] The role of conventional imaging methods, *e.g.*, CT and MRI in the differential diagnosis of pancreatic masses, was reported to be disappointing.[42,54,55] CT is the most used technique for diagnosis and staging of pancreatic cancer.[42,43,53,54,56] However, detection of SPL <20 mm is difficult using CT[51,57,58] and CT does not reliably allow differential diagnosis.[34,36,59]

The value of CE-EUS has been proven in a recently published (SPATEUS) study with data of 394 patients (median age: 61 years; range: 18–100 years; 158 males and 236 females) with small SPL ≤15 mm and a definite histological or cytological diagnosis. The inclusion criteria for this retrospective study analysis were small SPL ≤15 mm, which have been detected in asymptomatic patients with a final diagnosis based on histology or cytology obtained by imaging-guided biopsy and/or surgery.[34] Of 394 patients with small SPLs, 146 (37%) were finally diagnosed as PDAC (median age: 66 years; range: 31–100 years; 55 males and 91 females). All but one patient were operated. In the whole population of small SPL, the PDAC prevalence was 146/394 (37%). In the subgroup of SPL, measuring exactly 15 mm (n = 83), 51 lesions proved to be PDAC (62%). In contrast, only 95 of 311 SPLs <15 mm (31%) were diagnosed to be PDAC (P < 0.01). Approximately 60% of small SPLs were finally diagnosed with lesions other than PDAC, which is important to know before radical surgery.[34] In a small subgroup of patients (n = 38), we were able to evaluate the contrast behavior of PDAC and neuroendocrine tumor (NET) with CT in comparison with CE-EUS. Noteworthy, in 37% of patients, CT was not able to detect an SPL. This might be due to the very small diameter of these lesions (median 8 mm), which however had been described and characterized before by EUS and CE-EUS only. According to the small number of patients in this subgroup and the retrospective design of the study, this observed suboptimal consistency between CT and CE-EUS enhancement patterns must be interpreted with caution. Moreover, contrast enhancement patterns with CT might have been influenced by sequelae of the previously performed biopsy (*e.g.*, hemorrhage).

In addition, a meta-analysis has proved the high accuracy of CE-US and CE-EUS to discriminate between PDAC and other SPL with a high accuracy of nearly 90%, concluding that CE-US and CE-EUS should be used as first-line methods for characterizing neoplastic pancreatic lesions.[60]

THE PROBLEMS OF EARLY DETECTION

In patients with solid pancreatic lesions (SPLs), a diameter of ≥15 mm is predictive of PDAC and in lesions >25 mm in more than 90% of patients PDAC. A lesion size <15 mm is predictive for etiologies other than PDAC.[34,58] Therefore, there is a need for differential diagnosis of small SPL. CE-EUS has proven to differentiate PDAC from other SPL by analyzing the enhancement pattern.[30,33,34,44,61] PDAC is typically hypovascular and, therefore, hypoenhancing in all phases because of the low mean vascular density.[6,30,31] The presence of intratumoral fibrosis and necrosis is typical for the highly aggressive types with reduced microvascular density and perfusion.[34,62] In the SPATEUS study population, 92% of PDAC ≤15 mm were hypoenhancing with CE-EUS.[34]

Most other differential diagnoses of SPL such as NETs,[34,44] solid serous microcystic neoplasia with only microscopically detectable cysts mimicking solid lesions, metastases (*e.g.*, of renal cell cancer), lymphoma, mesenchymal tumors, pancreatic neoplasia of other origin, and intrapancreatic accessory spleens usually present as iso- or hyper-enhancing masses compared to the surrounding pancreatic parenchyma [Figure 1].[6,30-33]

SUMMARY

CE-EUS is mandatory for differential diagnosis of SPL. In principle, all SPLs are presumed to be PDAC if not otherwise proven and therefore radical surgery is recommended by guidelines[55,63-65] without biopsy and therefore, without prior histological or cytological verification unless contraindications are present or a strong suspicion of a specific diagnosis other than PDAC is raised due to patients history or ambiguous imaging results.[34,55] According to more recent studies, all hyperenhancing SPLs are biopsied because they are often of different etiology implying different management of patients.[6,34] EUS-FNA currently may be regarded the "gold standard" of the final diagnosis in small hypervascular SPL.[11-13,34,52,58,66-73]

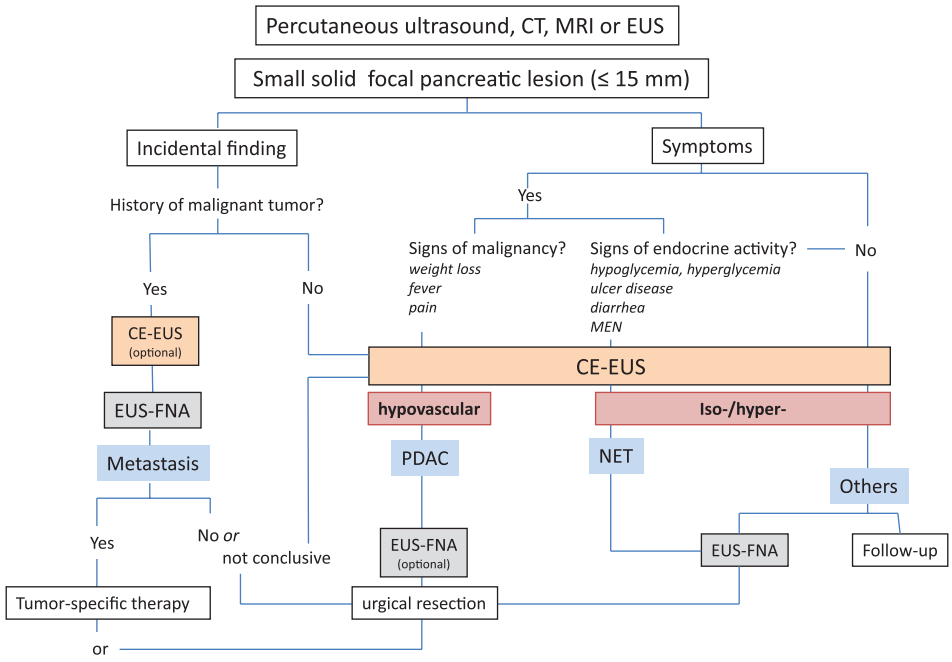

Figure 1. Diagnostic algorithm in small pancreatic lesions. CE-EUS: Contrast-enhanced endoscopic ultrasound, EUS-FNA: endoscopic ultrasound-guided fine needle aspiration, PDAC: Pancreatic ductal adenocarcinoma, NET: neuroendocrine tumor, CT: Computed tomography, MRI: Magnetic resonance imaging

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