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Transabdominal Contrast-Enhanced Ultrasonography of Pancreatic Cancer

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Key Words

Contrast-enhanced ultrasonography · Cystic pancreatic lesions · Pancreatic ductal adenocarcinomas · Pseudocysts · Ultrasonography

Abstract

Since its introduction, contrast-enhanced ultrasonography (CEUS) has significantly extended the value of ultrasonography (US). CEUS can be used to more accurately determine pancreatic lesions compared to conventional US or to characterize lesions already detectable by US. Thus, CEUS can aid in the differential diagnosis of pancreatic tumors. Using US contrast media, it is possible to visually detect microvessels in the majority of pancreatic ductal adenocarcinomas. Thus, the use of quantitatively evaluated transabdominal CEUS can help in the differentiation of patients with mass-forming pancreatitis from patients with pancreatic adenocarcinomas. In neuroendocrine pancreatic tumors, different enhancement patterns can be observed in relation to the tumor mass: larger ones show a rapid early enhancement sometimes combined with necrotic central structures, and smaller ones disclose a capillary-blush enhancement. Pseudocysts, the most widespread cystic lesions of the pancreas, are not vascularized. They do not show any signal in CEUS and remain entirely anechoic in all phases, while true cystic pancreatic tumors usually have vascularized septa and parietal nodules. In summary, CEUS is effective for differentiating solid pancreatic tumors in most cases. CEUS is safe and cost effective and can better discriminate solid from cystic pancreatic lesions, thereby directing further imaging modalities.

Introduction

Pancreatic carcinoma is an aggressive and devastating disease. It is characterized by invasiveness, rapid progression and profound resistance to treatment. Only 10–20% of patients with pancreatic cancer are diagnosed with tumors suitable for surgical resection, the only cure. Imaging of pancreatic tumors employs various techniques such as B-mode ultrasound (US), color Doppler sonography, endoscopic US, computed tomography (CT) and magnetic resonance imaging (MRI). Unfortunately, in up to 30% of patients determined to have a resectable tumor by preoperative imaging the lesion is deemed unresectable during surgery [1, 2].

US is usually the first approach to investigation due to its relatively low costs, noninvasiveness, and general availability. B-mode US allows for the identification of focal lesions, even small ones of ~1 cm in diameter, which

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are usually hypoechoic or cystic. Nevertheless, among these hypoechoic lesions, B-mode US is unable to discriminate adenocarcinomas from islet cell tumors or even rarer diseases, such as microcystic adenomas or focal pancreatitis. The advantages of CT and MRI include the ability to assess more lesion types during different dynamic phases.

Since its introduction in 1995, contrast-enhanced US (CEUS) has offered a wide array of diagnostic possibilities and has significantly extended the value of US. It has already proven to be a competent tool for evaluating the liver. However, other organs, particularly the pancreas, can be examined during continuous US imaging [3]. CEUS can be used to improve the visualization of pancreatic lesions compared to conventional US or to characterize lesions already detectable by US. CEUS provides high contrast and spatial resolution. Utilizing microbubbles, which represent an inherent contrast medium in the blood pool, perfusion of a tissue can be visualized without motion artifacts. Also, tumor enhancements can be seen more clearly by deleting background tissue signals and permitting dynamic observations in the same plane [3–5]. Together, these abilities make CEUS a sensitive imaging technique for estimating the vascularity of pancreatic lesions. Neoangiogenesis and residual tumors can be precisely studied to assess treatment response because CEUS can visualize tumor vascularization [4–9]. In addition, it has been reported that CEUS imaging is superior to helical CT regarding the identification of pancreatic tumor vascularization [7].

Using US contrast media, it is possible to visually detect microvessels in the majority of pancreatic ductal adenocarcinomas (PDACs). A previous study found a sensitivity of 95% for the detection of carcinomas [10]. However, using this technology, the subjective assessment of the degree of vascularization still remains problematic because the examiner must make a judgment based on a personal impression of brightness and contrast compared to the surrounding tissue. In addition, interindividual comparisons are not possible using this method. However, software algorithms can be used to quantify changes in contrast intensity. Thus, objective information can be obtained for the entire contrast-enhanced examination. In one of our recently published studies [11], the use of quantitatively evaluated transabdominal CEUS enabled the differentiation of patients with mass-forming pancreatitis from patients with pancreatic adenocarcinomas. Thus, CEUS can notably improve the accuracy of US, leading to a better recognition and description of pancreatic lesions [4–9]. Additionally, *endoscopic* CEUS has also been described as a useful tool for the differential diagnosis of pancreatic lesions in patients with chronic pancreatitis [12–14].

Compared to CT and MRI, the CEUS technique is simple and inexpensive. It is noninvasive and can be accomplished in an outpatient setting. It can also be performed on patients with renal failure or patients allergic to iodine contrast agents [3, 15]. Contrary to the contrast agents used in CT or MRI, US contrast agents are generally well tolerated. In a study of >23,000 applications of US contrast agents, only 29 cases of adverse events were reported, and these were mostly minor complaints such as rash or pruritus. Of all the adverse events, only 2 anaphylactic reactions were graded as serious, and both resolved completely without permanent damage [16]. Thus, CEUS is generally contraindicated in patients who may develop fatal anaphylactic reactions, e.g. in patients with a history of unstable cardiac conditions.

At present, the application of CEUS is not part of the regular diagnostic routine applied for pancreatic cancer. It may be a tool for evaluating pathologic changes in pancreatic cancer and may provide useful information for staging before treatment [17].

Technical Background

Harmonic imaging with low acoustic pressure US is necessary for CEUS. Immediately after the injection of a second-generation contrast medium, the dynamic surveillance of the contrast-enhanced phases begins (early arterial, arterial, pancreatic, and late). Sulfur hexafluoride microbubbles can enter the microcirculation because of their low mean diameter of 2.5 μm [3]. The enhancement peaks between 15 and 20 s after the injection of the contrast medium. Pancreatic parenchymography is earlier and shorter than that of the liver due to the absence of portal venous blood supply. Afterwards, there is a progressive washout of contrast medium, with a loss of gland echogenicity [3]. According to our previous research, the mean arrival time in healthy volunteers is 14 s; the time to reach peak intensity was measured at 22 s, and the maximum intensity was 5.3 dB on average [11]. These times can be considerably longer when measuring the contrast phase in pancreatic tumors or chronic pancreatitis. However, technical problems such as restricted image resolution of deep regions and poor sonographic imaging of the pancreas due to overlying abdominal gas or fat can often impair the contrast-enhanced evaluation of the pancreas [3, 5].

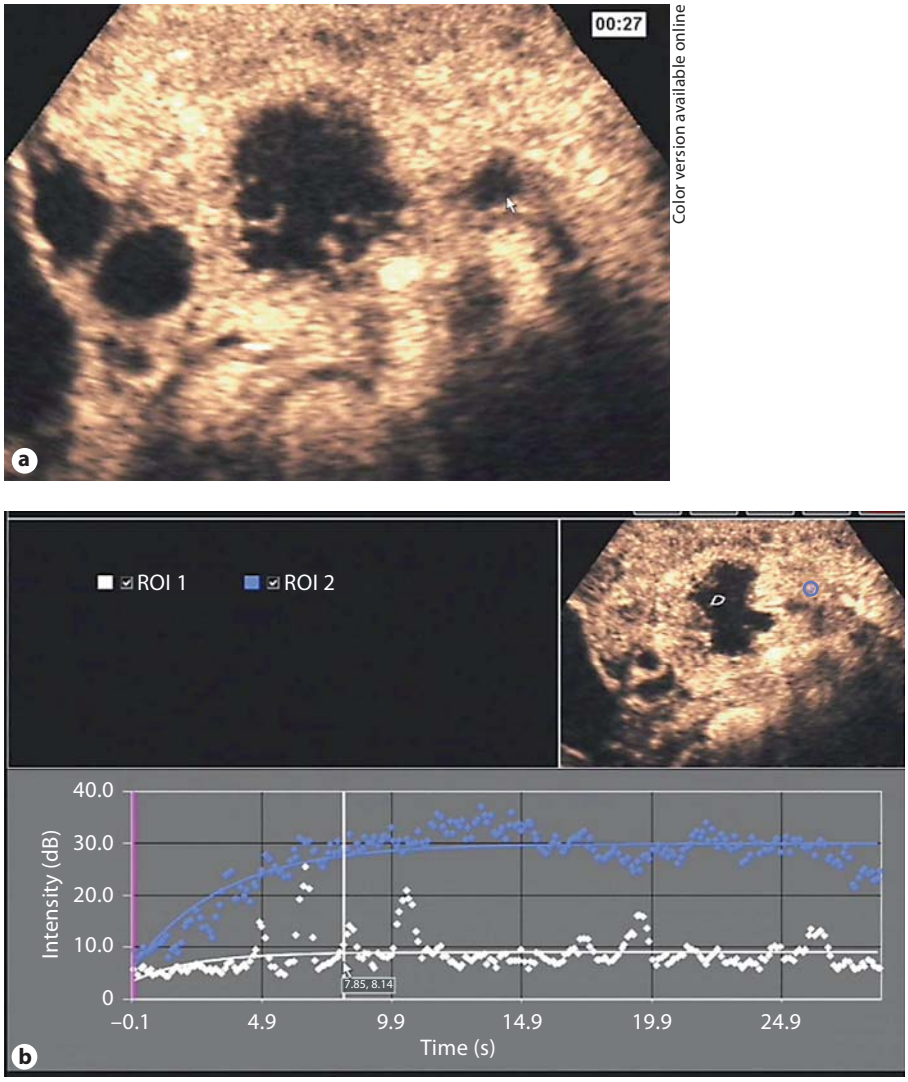

Fig. 1. a PDAC in the pancreatic head. CEUS using 1.2 ml of SonoVue® in low-mechanical index mode, 27 s after injection. **b** Quantification of the contrast course. Regions of interest (ROIs) are defined within the center of the tumor and within the surrounding normal tissue.

Clinical Applications of CEUS for Pancreatic Tumors

Focal lesions that are hypoechoic on B-mode US can be classified by CEUS as hypo-, iso-, or hyperechoic according to their enhancement compared to that of the adjacent parenchyma.

Ductal Adenocarcinoma

Ductal adenocarcinoma is the type of pancreatic tumor most frequently diagnosed. This pancreatic tumor usually shows a hypoenhanced/hypoechoic appearance in CEUS compared to the adjacent pancreatic tissue in all phases because of poor tumor vascularization [17]. The margins and size of the lesion are better visible than with B-mode US (fig. 1). The correlation with peripancreatic arterial and venous vessels can also be evaluated for local staging [5, 7, 9, 18]. Tumors for which the size of the hypoechoic area is unaffected in CEUS have clear margins with no infiltration or inflammation. Tumors for which the size of the hypoechoic area is reduced in CEUS have indistinct margins with infiltration of cancerous cells and inflammation.

The illustration of tumor margins by CEUS is more precise at low enhancements rather than high ones [18]. High enhancement patterns of ductal adenocarcinomas by CEUS correlate with a low potential for determining resectability. In cases of well-differentiated carcinoma, the mass tends to be iso- or hypovascular compared to

the remaining parenchyma, and the margins of the tumor are hard to evaluate. On the contrary, a confirmation of resectability can be precisely obtained by CEUS in the presence of hypovascular pancreatic tumors. In this case, the border between the tumor and the normal neighboring pancreatic parenchyma is more clearly defined. Therefore, the pattern of pancreatic adenocarcinoma enhancement influences the image of tumor margins obtained by CEUS [18].

Pancreatic carcinomas sometimes appear isoechoic. This pattern is a result of the moderate vascularization occurring in some histotypes (e.g. anaplastic and acinar-cell carcinomas) [19]. The isoechoic pattern is also frequent in focal pancreatitis [20]. Consequently, CEUS cannot always accurately distinguish between adenocarcinoma and focal pancreatitis, similar to CT and MRI [21]. However, supplemented with quantification software, data helpful for a differential diagnosis can be obtained (fig. 1b). The mean arrival time for carcinoma lesions is reached on average 13 s later than in the normal pancreatic tissue of the same patient. On average, it takes 34 s longer to reach the measured peak in PDACs than in normal tissue, whereas the peak for mass-forming chronic pancreatitis is similar or only slightly longer than in normal tissue [11].

Modern helical CT scans are generally accepted as the standard for the staging of PDACs. The improved ability of CEUS to demonstrate intratumoral vessels may be the reason why the common, well-vascularized aspects of PDAC are exposed by this imaging method. The use of CEUS may add significant information for the regional staging of pancreatic adenocarcinoma [22] by confirming vascular infiltration or encasement by the neoplasm. Furthermore, CEUS may enhance sensitivity and specificity in the identification and characterization of liver metastases, especially in the detection of very small lesions [23]. In practice, after studying a pancreatic lesion in the arterial, pancreatic, and venous phases, liver metastases can be detected using the late hepatic contrast-enhanced phase [5].

Endocrine Tumors

Endocrine islet cell tumors usually appear hyperechoic/hypervascular in the arterial phase of imaging due to their rich vascularization [24]. A differential diagnosis between endocrine tumors and ductal adenocarcinomas through imaging is of great value. Interestingly, different enhancement patterns can be observed in relation to the mass of tumors and tumor vessels. Voluminous endocrine tumors show a rapid and powerful enhancement in the early contrast-enhanced phases, with the exclusion of necrotic intralesional areas [19, 24, 25]. In moderately sized neuroendocrine pancreatic tumors, a capillary-blush enhancement can be seen in the early contrast-enhanced phase. Nonfunctioning neuroendocrine tumors may be hypovascularized, depending on the amount of stroma within the thick and hyalinized lesion. In some pancreatic neuroendocrine tumors, a hypodense image is visible on CT, whereas a clear enhancement is noticeable in CEUS [25]. The ability of CEUS to demonstrate endocrine tumor vascularization is a consequence of the high resolving power combined with the blood pool circulation of the microbubbles; therefore, the real-time dynamic mode allows depicting vascularization in a way that CT and MRI do not permit. A similar CEUS pattern can also be observed in hypervascular metastases (from renal cell carcinomas and melanomas) [19].

Cystic Tumors

CEUS improves the US differential diagnosis between pseudocysts and cystic tumors of the pancreas by revealing the vascularization of intralesional inclusions. Pseudocysts, the most widespread cystic lesion of the pancreas, are nonvascularized. They do not show any signal in CEUS and remain entirely anechoic in all phases, even if they appear inhomogeneous by US. In some cases, larger, peripancreatic vessels may be seen inside the pseudocyst. True cystic pancreatic tumors usually have vascularized septa and parietal nodules [26]. A simple, imaging-based classification of pancreatic cystic lesions has been proposed. Herein, there are four types: microcystic, unilocular, macrocystic, and cystic with a solid component [27].

Serous cystadenomas have a benign biological behavior in the great majority of cases. The most common type of serous cystadenoma is the microcystic type, macroscopically marked by multiple small cysts divided by thin septa. The margins are well defined, and a central scar may be present. B-mode US can be used to characterize serous microcystic adenomas if they demonstrate a typical honeycomb appearance [27, 28]. In CEUS, intralesional septal enhancement and the absence of papillary projections improve the recognition of microcystic features of the lesion and improve diagnostic accuracy. In the case of small lesions that do not require surgical intervention, CEUS results do not require further verification by CT and/or MRI.

Less common oligocystic or macrocystic types of serous cystadenomas present features that may be impossible to distinguish from those of other pancreatic macrocystic tumors [4, 29]. Unilocular single cysts without

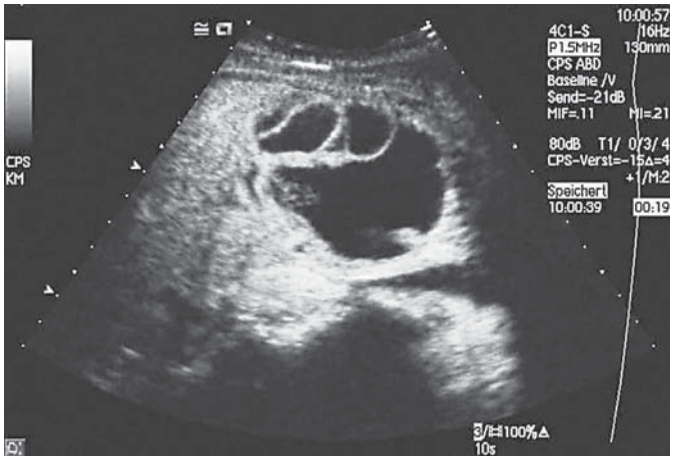

Fig. 2. Cystic tumor of the pancreas. The perfusion of the septae by CEUS and the vascularized nodules are suggestive of MCN or IPMN.

internal septa, solid components, and parietal or central calcifications on B-mode US can be classified as pseudocysts, oligocystic serous cystadenomas, mucinous cystic neoplasms (MCN), or intraductal papillary mucinous neoplasms (IPMN) [27]. Here, CEUS does not yield any additional diagnostic information. Specifically, CEUS imaging cannot show a communication with the pancreatic duct in the way that MR cholangiopancreatography or CT can do [30]. Similarly, when two or more unilocular cysts are present, the differential diagnosis between pseudocysts and IPMNs [27] cannot be made by CEUS, and the use of CT or MRI is required.

Cysts with a solid component on B-mode US may be either unilocular or multilocular. True cystic tumors (MCN and IPMN) and solid tumors with a cystic region or cystic degeneration – primary or metastatic – are included in this group. All tumors of this group are either malignant or have a high malignancy potential [27]. Again, the use of CEUS cannot provide an important diagnostic contribution in these cases.

Macrocystic lesions include multilocular cysts with fewer and larger (>2 cm) compartments than serous microcystic adenomas [27]. This class includes MCN and IPMN. A thick wall, thick septae, and mural or septal calcifications are the most important findings associated with malignancy [27, 30]. In these cases, although CEUS permits better imaging of the wall and septae [6], it does not provide a significant diagnostic advantage over B-mode US (fig. 2).

Discussion

The role of imaging methods in the differential diagnosis of pancreatic tumors has been reported as unsatisfactory [7, 31–37]. Consequently, a method with both high sensitivity and high specificity for tumor differentiation is needed due to the fact that tumor differentiation is essential for appropriate therapy and a favorable prognosis. The vascular patterns of pancreatic tumors have been examined in patients with cystic and solid tumors using earlier second-harmonic imaging and other contrast-enhancing techniques with promising, but also conflicting, results [6, 7, 10, 20, 29, 32, 38–48].

In most tumors, the degree of vascularity compared to the adjacent pancreatic parenchyma is helpful for tumor description. Tissue perfusion is altered by histological interstitial changes caused by the underlying disease. Because tumors can only be nourished by diffusion up to a distance of 1–2 mm, tumor growth is highly dependent on the development of nutrient-supplying tumor vessels. These vessels are mostly capillaries between 5 and 8 μm in diameter, and, histologically, they consist only of an endothelial layer without any surrounding smooth muscle cells [43]. Thus, the analysis of pathological perfusion patterns can aid in the differential diagnosis of lesions. However, none of the conventional imaging methods (unenhanced US, CT, MRI, angiography, or positron emission tomography) can sufficiently visualize microvascularization of vessels with a diameter <10 μm and a flow <1 mm/s [49] because they are considerably smaller than the resolution of these imaging techniques, including angiography. With CEUS, this barrier has been overcome; although the capillary net is not anatomically visible, microbubbles in the capillary perfusion can be observed as contrast enhancement [50] and, thus, quantitatively measured.

CEUS can distinguish between frequently hypovascularized malignant ductal adenocarcinomas and hypervascularized tumors, typically neuroendocrine tumors and serous microcystic adenomas of the pancreas. This differential diagnosis is of great value because serous microcystic adenomas do not require surgery in the majority of cases due to their very low malignancy potential. In addition, neuroendocrine tumors progress slowly and adjuvant treatment is available. Local resection of peripherally located tumors is an optional treatment, or resection may be less radical than required according to oncological criteria for ductal adenocarcinomas.

CEUS techniques have been found to be beneficial in the differential diagnosis of chronic pancreatitis and duc-

tal adenocarcinomas, but results depend on the tools and methods employed. For ductal adenocarcinomas, only arterial vessels are displayed using power Doppler CEUS. Chronic pancreatitis displays both arterial and venous vessels equally [13]. These differences result from the different patterns of histopathological changes. In case of chronic inflammation, hemorrhages or thromboses lead to scarring and shrinkage of the entire gland and result in a fragmented circulation pattern. PDACs, in contrast, show a network of capillary vessels surrounding the tumor. Blood flows from the periphery to the core of the tumor and arteries are primarily found along the tumor margins, so that the contrast agent flows through a ring of vessels and only subsequently reaches the central structures.

Conventional imaging modalities (unenhanced US, CT, MRI, angiography, and positron emission tomography) cannot adequately visualize the microvascularization specific for the nutrient supply of the tumor. The use of CEUS allows a better identification of vascularization of solid pancreatic tumors than spiral CT [19, 48]. Comparing CEUS and CT scans with a histological image, a significantly better correlation exists between the histological tumor vascularization described by the CEUS image than that of the CT scan. Tumor vascularity is always underestimated in a CT scan [19, 42], and significantly smaller 'necrotic' areas may be visualized by CEUS but not in the corresponding CT scan [51].

There may be several reasons for these results: first, the kinetics of US and CT contrast agents are different because US contrast agents remain within the vessels while CT contrast agents disperse into the parenchyma. Second, in CEUS, vascularity is assessed in a dynamic, real-time fashion comparing imaging before, after, and during the administration of the contrast media, whereas in a CT scan the contrast of the lesion is compared with the surrounding tissue. Third, CEUS enables repetitive examinations of the same area with different settings and different contrast phases and can thus lead to more differentiated information regarding tumor perfusion.

The differentiation of inflammatory pseudotumors in chronic pancreatitis and PDAC has been attempted by several groups. Koito et al. [32] showed that CEUS had a higher sensitivity for the confirmation of vascularization than CT and digital subtraction angiography. Similar results were reported by Becker et al. [52], who demonstrated a sensitivity of 94% and a specificity of 100% with CEUS for the differentiation between PDAC and inflammatory pseudotumors. For this differentiation, and without the possibility of simultaneous 'macroscopic' imaging, the accuracy of angiography alone was only 50%. Additionally, the resolution of digital subtraction angiography is insufficient for the imaging of capillary perfusion [53, 54]. In CEUS, however, microbubbles in the capillary network can be detected as an increase in contrast, which, with appropriate software, can be quantified with a sensitivity that is unachievable by visual observation alone. The use of quantification software strongly supports the visual observation of a contrast examination, and the software can be used to calculate parameters characteristic for a contrast course within lesions and normal parenchyma that can help to distinguish pancreatic tumors.

In summary, the successful management and treatment of pancreatic tumors requires highly sensitive and specific imaging techniques. CEUS is effective for differentiating solid pancreatic tumors in most cases. Characteristics of a variety of pancreatic lesions are well identified by contrast-enhanced CT or MRI, but only CEUS is able to visualize them in real time. Because CEUS more accurately determines pancreatic diseases than baseline US, it can directly result in a better diagnostic workup and treatment, especially compared to CT or MRI. CEUS is safe and cost effective and can better discriminate solid from cystic pancreatic lesions, thereby directing patients towards a CT if the lesion is solid and towards an MRI if the lesion is cystic.

Nevertheless, histology is still the standard reference for the differentiation of pancreatic lesions; however, this can still result in false-negative results if the specimens obtained are not representative. A transabdominal or endosonographically guided endoscopic biopsy is suggested for patients with hypervascular lesions and suspected nonfunctional neuroendocrine tumors or serous microcystic adenomas. Biopsy is helpful because the therapeutic approach to iso- and hypervascular lesions should be different from that used for the most common hypovascular PDACs. In patients with serous cystadenomas, close follow-up might be suggested, whereas nonfunctional neuroendocrine tumors will require surgery due to their malignancy potential. Hypovascular pancreatic lesions in patients without a contraindication (e.g. liver metastases or peritoneal metastases) should undergo surgery without a prior biopsy due to the fact that these imaging findings are indicative of PDACs. For cases who are not offered surgery due to metastases or other reasons, a biopsy yielding cytology prior to palliative chemotherapy is required. Most of the other very rare entities are also hypervascular, and a biopsy is mandatory for individualized therapeutic strategies, typically resulting in resection.

The potential for new indications for CEUS is high, particularly for pancreatic diseases for which the treatment regimen is currently based on CT, MRI, endoscopic US, or a mixture of these techniques. Over the last few years, these assessments have been increasingly harmonized and, in some cases, replaced by CEUS. In conclusion, additional prospective studies would be desirable to compare CEUS to other imaging modalities such as CT and MRI in diverse pancreatic diseases, aiming to better classify its role in the diagnosis, management, and follow-up of pancreatic diseases.

Disclosure Statement

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