SIUMB recommendations for focal pancreatic lesions

Mirko D’Onofrio1 · Ilario de Sio2 · Paioletta Mirk3 · Gianpaolo Vidili4 · Michele Bertolotto5 · Vito Cantisani6 · Cosima Schiavone7 · The SIUMBexperts committee

Received: 27 July 2020 / Accepted: 4 August 2020 / Published online: 4 September 2020 © The Author(s) 2020

Abstract
Contrast-enhanced ultrasonography (CEUS) is increasingly being performed in Italy and Europe, particularly in the field of hepato-gastroenterology. Initially, it was mainly carried out to characterize focal hepatic lesions, but, since then, numerous studies have demonstrated its efficacy in the differential diagnosis of focal pancreatic pathologies (D’Onofrio et al. in Expert Rev Med Devices 7(2):257–273, 2010; Vidili et al. in J Ultrasound 22(1):41–51, 2019). The purpose of this paper is to provide Italian Medical Doctors with recommendations and thereby practical guidelines on the management of these patients. The present paper reports the final conclusions reached by the SIUMB guideline commission. This paper addresses particularly percutaneous ultrasound (US) examination (transabdominal US) and is drawn up specifically for publication.

Keywords Pancreas · Ultrasound · Pancreatic cancer · Pancreatic cystic lesions · Contrast-enhanced ultrasound · CEUS · Pancreatic biopsy · Pancreatic cancer · Pancreatic adenocarcinoma

Background
Contrast-enhanced ultrasonography (CEUS) is increasingly being performed in Italy and Europe, particularly in the field of hepato-gastroenterology. Initially, it was mainly carried out to characterize focal hepatic lesions, but, since then, numerous studies have demonstrated its efficacy in the differential diagnosis of focal pancreatic pathologies [1, 2]. The purpose of this paper is to provide Italian Medical Doctors with recommendations and thereby practical guidelines on the management of these patients. The present paper reports the final conclusions reached by the SIUMB guideline commission.

A bibliographic search for focal pancreatic lesions was carried out on PubMed using the following search terms: 2006–2016:

- "contrast enhanced ultrasound".
- "pancreatic cancers".
- "pancreatic adenocarcinoma"/"adenocarcinoma".
- "pancreatic neuroendocrine tumors"/"endocrine tumors".
- "pancreatic cystic lesions"/"cystic lesions".

The search led to the identification of 879 articles. Activating a filter for clinical trials, reviews, and meta-analyses, the number was reduced to 397 articles.

We proceeded with filtering these papers by including only:

- studies conducted on humans;

The SIUMB experts’ committee members are listed in Acknowledgements.

The SIUMB experts’ committee members are listed in Acknowledgements.
• studies in which the performance of CEUS in the characterization of pancreatic lesions was evaluated and sensitivity/specificity or positive/negative predictive values (PPV/NPV) were reported;
• studies in which Sonovue was used (data related to Sonazoid and Definity were excluded, as these contrast agents are not used in Italy);
• studies providing a qualitative evaluation of the contrast agent (we excluded studies providing a quantitative evaluation based on wash in/wash out times or image interpretation using software such as Photoshop etc.);
• studies of at least 30 patients (at least 10 benign pancreatic lesions and 10 malignant pancreatic lesions);
• studies published in English;
• studies in which histology, computed tomography (CT), and/or magnetic resonance imaging (MRI) and/or clinical examination (clinical–radiological follow-up) were considered as the gold standard.

This further skimming led to the evaluation of 1 clinical trial, 3 reviews, and 2 meta-analyses. The document produced on the basis of the selected studies was presented to a panel of experts gathered on 17 November 2019 to discuss and vote on each single point/recommendation.

This paper addresses particularly percutaneous ultrasound (US) examination (transabdominal US) and is drawn up specifically for publication.

Pancreas

When a pancreatic lesion is detected, an immediate differential diagnosis is essential to proceed with appropriate management. Incidental detection of a pancreatic lesion occurs quite frequently in some countries (e.g., the United States).

Focal pancreatic lesions identified at the conventional US examination can be studied by CEUS to improve tissue characterization: solid pancreatic lesion vs cystic pancreatic lesion [1].

Approval 84%

Although the role of elastosonography is not yet well defined, its use in pancreatic lesions to improve the management is reported in the literature [3].

After US detection of one or more focal cystic lesions of the pancreas, the patient should be submitted directly to MRI as a second-line examination to obtain further diagnostic information.

Approval > 90%

Contrast-enhanced endoscopic US (CE-EUS)

CE-EUS can be recommended to [4]:

1- Improve characterization of pancreatic ductal adenocarcinoma on the basis of the hypovascular pattern mainly using CE-EUS and color Doppler (LoE 1b, GoR A).
2- Discriminate between chronic mass-forming pancreatitis and ductal adenocarcinoma in patients with chronic pancreatitis (LoE 1a, GoR A).
3- Improve discrimination between pancreatic cystic tumors and pancreatic pseudocysts (LoE 1b, GoR A).

Elastosonography

1- Endoscopic US (EUS) elastography is useful as a complementary tool in the characterization of focal pancreatic lesions [3].
2. If there is a strong clinical suspicion of pancreatic cancer in the presence of inconclusive or negative biopsy outcome, detection of a “hard” focal lesion at elastography, and/or a suspicious mass indicating neoplasia at CE-EUS (hypovascular lesion), this should guide the clinical management suggesting a repeated EUS fine needle aspiration (FNA) or referring the patient directly to surgery [3, 5].

3. At the present time, EUS elastography cannot be recommended for differentiation between advanced chronic pancreatitis and pancreatic ductal adenocarcinoma as both diseases cause similar tissue “hardness” in an elevated number of cases [3].

**Approval 100%**

**Focal pancreatic lesions**

**Pancreatic adenocarcinoma**

- CEUS can be a first-line diagnostic tool in the characterization of pancreatic ductal adenocarcinoma.
- In contrast-enhanced examinations, pancreatic adenocarcinoma shows a typical poor enhancement due to a strong intralesional desmoplastic reaction, which causes low mean vascular density and very poor perfusion.
- In patients with an easily explored pancreatic region, sensitivity of CEUS in the diagnosis of ductal pancreatic adenocarcinoma is adequate and does not differ statistically from that of contrast-enhanced CT. Comparison of diagnostic sensitivity of CEUS and contrast-enhanced CT reported in the literature shows that there is no statistically significant difference between the sensitivity of the two techniques. CEUS and contrast-enhanced CT provide the same possibility of diagnosing pancreatic adenocarcinoma. The combination of CEUS and contrast-enhanced CT can increase diagnostic performance and provide an early diagnosis of ductal adenocarcinoma.
- US/CEUS limitations are not linked to the size of the tumor, but to the technique and the patient’s condition including meteorism and constitutional factors.
- CEUS is a safe and feasible method providing an immediate and more accurate characterization of pancreatic lesions and possible liver metastases detection.
- In a meta-analysis, the overall sensitivity (0.89 [95% CI 0.85–0.92]), specificity (0.84 [95% CI 0.77–0.89]), and diagnostic odds ratio (DOR) (61.12 [95% CI 34.81–107.32]) highlighted the outstanding ability of CEUS in the characterization and distinction between adenocarcinoma and other pancreatic pathologies [6].
- All lesions appearing solid at conventional US and hypovascular at CEUS should be considered ductal adenocarcinomas until proven otherwise.

**Approval 100%**

- The results reported in the literature confirm the reliability of US in case a small pancreatic nodule is detected and characterized by CEUS as adenocarcinoma, even if subsequent CT outcome is negative. The finding should be assessed using MRI or EUS. Thus, if a small pancreatic nodule is incidentally detected at US imaging with or without contrast enhancement, the patient should be referred directly to MRI to obtain a prompt diagnosis of ductal adenocarcinoma.
- CEUS is a sensitive method for detecting liver metastases and can be decisive in case of small liver lesions.

**Approval >95%**

According to the recent guidelines, CEUS may become the first-line diagnostic tool in the characterization of pancreatic ductal adenocarcinoma detected by means of ultrasound [4]. The main advantage of CEUS over other diagnostic methods is the possibility of obtaining a real time dynamic study of the pancreatic gland by using blood pool contrast agent [7]. The study procedure is focused on real-time evaluation of a pancreatic lesion after US contrast injection. In particular, an arterial phase can be observed, which has a duration of 10–30 s followed by a venous phase lasting from 30 to 120 s. In contrast-enhanced examinations, pancreatic adenocarcinoma shows a typical poor enhancement due to a strong intralesional desmoplastic reaction, which causes low mean vascular density and a very poor perfusion [8]. In a study, D’Onofrio et al. compared diagnostic sensitivity of US/CEUS and contrast-enhanced CT. They found that there is no statistically significant difference between the sensitivity of the two techniques (p = 0.678), i.e., CEUS and contrast-enhanced CT provide the same possibility of diagnosing pancreatic adenocarcinoma. However, some discordant points between the two methods emerged from this study: 9.77% of the total patient population, particularly patients with small pancreatic lesions (4 lesions out of 13 measured < 2 cm; 7 lesions out of 13 measured 2–3 cm), were diagnosed only at US/CEUS. These data are in agreement with the current scientific literature, which shows that 10% of pancreatic ductal adenocarcinomas are isodense compared to the surrounding gland, and moreover, that the prevalence of isodense tumors on contrast-enhanced CT is greater in lesions < 2 cm [9, 10].

In view of these conclusions, it is clear that the combination of US/CEUS and contrast-enhanced CT can increase diagnostic accuracy and provide an early diagnosis of ductal adenocarcinoma. On the other hand, 9 lesions were diagnosed only at contrast-enhanced CT: in 2 cases, US/CEUS did not identify focal lesions, and in 7 cases, US/CEUS showed different echoic features compared to the typical enhancement pattern, and CT showed 7 lesions > 3 cm. US/
CEUS limitations are not linked to the size of the tumor, but to the technique and the patient’s condition including mete-roism and constitutional causes. All this confirms that the combination of US/CEUS and contrast-enhanced CT contributes to more accurate diagnostic results. In conclusion, in patients with an easily explored pancreatic region, sensitivity of US/CEUS in the diagnosis of ductal pancreatic adenocarcinoma is adequate and does not differ statistically from that of contrast-enhanced CT. US/CEUS sensitivity seems to be higher in small- and medium-sized lesions, whereas contrast-enhanced CT sensitivity is higher in larger lesions. A combination of the two methods can thus provide a greater diagnostic accuracy in patients with pancreatic ductal adenocarcinoma [11].

CEUS has proved to be an accurate imaging method for evaluating the vascularity of pancreatic lesions and in the differentiation between solid and cystic lesions, thereby influencing the choice of subsequent diagnostic investigations in order to obtain a useful, immediate, and faster diagnosis [3, 11, 12]. In pancreatic ductal adenocarcinoma, a rapid diagnosis is very important. Although CEUS is relatively new in the evaluation of the pancreas, it is a safe and feasible technique which provides a better and immediate characterization of the lesion and permits staging of the neoplasm during US examination [13]. The primary objective of the meta-analysis carried out by D’Onofrio et al. was to evaluate the diagnostic ability of CEUS to identify and characterize typically hypovascularized pancreatic ductal adenocarcinomas. The merit of CEUS lies mainly in the ability to differentiate pancreatic adenocarcinoma from other masses of a different etiology but with a similar appearance on conventional US image, thanks to the dynamic evaluation allowing a direct observation of the post-contrast agent impregnation pattern, suggesting other possible diagnoses in case of isovascularized or hypervascularized lesions. In this meta-analysis, the overall sensitivity (0.89 [95% CI 0.85–0.92]), specificity (0.84 [95% CI 0.77–0.89]), and diagnostic odds ratio (DOR) (61.12 [95% CI 34.81–107.32]) support the ability of CEUS to characterize the lesions, particularly smaller lesions < 2 cm with high accuracy. In agreement with the scientific literature and our previous experience, detection of a small pancreatic adenocarcinoma is difficult at CT in the absence of mass effect. In conclusion, the results obtained in this study, which are in agreement with the data reported in the literature, support the credibility of US if a small pancreatic nodule is detected and characterized as adenocarcinoma at CEUS, also in the presence of a subsequent negative outcome of CT. In that case, the lesion requires further investigation using MRI or EUS. Therefore, if a small pancreatic nodule is detected at US examination, the patient should be referred directly to MRI to obtain the benefit of a fast diagnosis of pancreatic ductal adenocarcinoma.

In a large multicenter study of 1439 pancreatic lesions, D’Onofrio et al. correctly characterized solid pancreatic lesions reaching an accuracy of 91.7%. Particularly, pancreatic ductal adenocarcinoma was correctly characterized reaching an accuracy of 87.7% on the basis of hypovascular appearance at CEUS. This means that all solid lesions detected at conventional US and appearing hypovascular at CEUS should be considered ductal adenocarcinomas until proven otherwise. In other series of histologically proven ductal adenocarcinomas including more than 50 cases, ductal adenocarcinoma was reported to be hypovascular in 73–93% of cases [14–16]. CEUS outcome was accurate in demonstrating hypervascularization of endocrine tumors.

In a multicenter study (PAMUS, see below), the accuracy of CEUS in characterizing neuroendocrine tumors was 90.5%. Also other interesting data are reported regarding
the characterization of cystic lesions, as cystic tumors and pseudocysts were correctly diagnosed by CEUS reaching an accuracy of 97.1% and 99%, respectively. In this study, the highest level of accuracy of CEUS compared to conventional US was thus achieved in the characterization of pancreatic lesions, showing a statistically significant difference ($p < 0.0001$) in the relative receiver-operating characteristic (ROC) curves. In conclusion, CEUS can increase the accuracy of US in the study of incidentally detected pancreatic masses, thus leading to a faster diagnosis. CEUS can acquire also other roles that may become the objects of further investigation: first, it can contribute to a better management of lesions detected at the conventional US examination; second, it can become a problem-solving method [17].

US is the first-line imaging method used in patients with symptoms suggesting malignant pathology of the pancreas. However, US sensitivity is markedly reduced in very small tumors, and the use of US contrast agent does not improve the detection of pancreatic nodules depending on gland exploration and nodule size. On the other hand, the use of US contrast agent improves diagnostic power of the method by allowing a highly accurate characterization of ductal adenocarcinoma [16]. Finally, in addition to determining local spread of the tumor using B-mode US and color-Doppler US evaluation, which should always be performed before CEUS, the method can detect liver metastases and be decisive in case of small liver lesions [18, 19].

**Neuroendocrine tumors**

- CEUS is significantly more accurate than the conventional US in the diagnosis of nonfunctional neuroendocrine tumors of the pancreas [20].
- CEUS is more sensitive than the conventional US in identifying liver metastases caused by neuroendocrine cancer.

**Approval 100%**

US combined with CT and/or MR cholangiopancreatography (MRCP) is recommended. The decision to carry out CT or MRI depends on the preference, skill, and experience of the radiologist and the availability of equipment in the individual institutions. Somatostatin receptor scintigraphy has so far been indicated as the main single screening method in the assessment of extrahepatic localizations. However, positron emission tomography (PET)-CT with Ga$^{68}$ and F$^{18}$-DOPA seems to be an interesting method able to provide a better resolution and detect more lesions. Patients with small non-functional neuroendocrine tumors of the pancreas should undergo EUS, as EUS-guided FNA biopsy has yielded good results in confirming the diagnosis. CEUS seems to improve the characterization of liver metastases caused by neuroendocrine tumors, and CE-EUS could prove effective in characterizing pancreatic endocrine tumors [20].

CEUS is significantly more accurate than the traditional B-mode US in the diagnosis of nonfunctional neuroendocrine tumors of the pancreas, showing correlation between CEUS enhancement pattern and Ki67 index [20, 21]. In addition, CEUS is more sensitive than the traditional US in identifying liver metastases caused by neuroendocrine cancer; these lesions appear at CEUS as irregularly hypervascularized lesions [20, 22].

**Pancreatic cystic lesions**

**Italian guidelines on cystic tumors** [23]

1. Conventional US of the pancreas cannot provide a definitive diagnosis of pancreatic cystic neoplasms (LoE 5, GoR D).
2. There are not enough detailed data in the literature regarding the use of CEUS in the differentiation between mucinous and non-mucinous pancreatic cystic lesions (LoE 5, GoR C).
3. MRI and contrast-enhanced CT are the first-line diagnostic techniques for differentiating between benign and malignant pancreatic cystic neoplasms. The performance of CEUS is similar to that of MRI and contrast-enhanced CT in pancreatic cystic lesions which are visible at US examination (LoE 1b, GoR).
4. There are no data in the literature supporting the role of percutaneous US-guided biopsy of pancreatic cystic neoplasms. FNA of these lesions should be carried out using the EUS approach (LoE 5, GoR D).
5. The role of each imaging method in the follow-up of asymptomatic patients with pancreatic cystic neoplasms depends on the size and number of lesions.
   - Small single cystic lesions (< 1 cm) visible on US image: US should be preferred until a change in size. If this occurs, CEUS or MRI should be performed to evaluate the presence of “suspicious” features. MRI with MRCP alternating with US should be used to evaluate the development of new cystic neoplasms of the pancreas. If MRI shows new cystic lesions, follow-up should be continued using MRI.
   - Small single cystic lesions (< 1 cm) that are not visible on US image: MR/MRCP (LoE 5, GoR D).
   - Large cystic lesions (≥ 1 cm) visible on US image: US should be preferred until a change in size. If this occurs, CEUS or MRI should be performed to evaluate the presence of “suspicious” features (dimensions, nodules, septa, contents, morphology). MRI with MRCP alter-
nating with US is currently performed to evaluate the
development of new cystic neoplasms.
- Large cystic lesions (≥ 1 cm) not visible on US image: MRI with MRCP or contrast-enhanced CT. In patients requiring close follow-up (3 months), contrast-enhanced CT should be performed in elderly patients only in the absence of renal insufficiency and/or in patients with absolute contraindications to MRI (LoE 5, GoR D).
- Multiple cysts: MRI with CPRM (LoE 5, GoR D).

Approval 100%

• In the presence of pancreatic cystic lesions easily explorable by US, the results of CEUS and MRI reported in the literature in detecting intralesional nodules and septa are very similar.
• CEUS should be considered a complementary imaging method in the characterization of pancreatic cystic masses detected at abdominal conventional US, and should, therefore, be included in the follow-up of borderline lesions.

Approval 100%

Visualization of tumor vascularization at CEUS is the direct result of the use of a contrast agent with intravascular distribution, a dynamic observation of the post-contrast phase, high spatial resolution, and of the current US contrast harmonic imaging. The ability of this method to cancel all signals coming from the background, so that the operator can see on the monitor only the intensity of the signal produced by the contrast agent passing under the US probe, while the non-vascularized tissues are not depicted, can easily be exploited in the evaluation of the walls and structure of pancreatic cystic lesions. The vascularized vital portions of pancreatic cystic tumors become progressively echoic during CEUS, while the contrast medium is passing through the capillary bed of the septa or the nodules inside the cysts. Intracystic debris, mucus, or blood clots, which are easily visible at the conventional US, are completely invisible in the post-contrast phase [8, 24]. For this reason, CEUS is reported to improve the characterization of pseudocysts [8, 24]. Moreover, due to the deletion of the underlying tissues and intracystic echoic contents (such as the mucinous contents), the detection rate of septa and nodules at CEUS is higher [22] than that of conventional US. During the conventional US, the viscosity of the mucin inside the lesion causes increased echogenicity, which may mask the internal wall thus leading to an incorrect diagnosis [8, 24]. The difference in diagnostic accuracy between CEUS and MRI in identifying septa and nodules is not significant. The data reported in the literature suggest that all patients with asymptomatic pancreatic cystic lesions without signs of suspected malignancy should be monitored. On the basis of these results, we believe that after an initial complete imaging assessment of a pancreatic cystic mass, the conventional US can be used as a follow-up method in lesions that do not require surgery. If changes are observed at the conventional US follow-up, CEUS can be performed. This would limit the use of MRI and CT, thereby reducing exposure to ionizing radiation and the costs. Data reported by D’Onofrio et al. showed that the results of CEUS and MRI in detecting intralesional septa and nodules are very similar in pancreatic cystic masses visible at abdominal US examination. CEUS should be considered a complementary imaging tool in the characterization of pancreatic cystic masses detected at abdominal conventional US and should, therefore, be included in the monitoring of borderline lesions. In the subgroup of patients whose cystic masses can be visualized at US, CEUS could be a less expensive imaging method, free of ionizing radiation, and effective in the monitoring of the lesions [25].

As regards the use of CEUS in pancreatic pathologies, the most recent update of the EFSUMB guidelines was drawn up in 2017 and published in 2018 [26].

Invasive diagnostics/US-guided needle aspiration/biopsy

Recommended guidelines INVUS (Guidelines on Interventional Ultrasound) [27]

1- In patients with resectable pancreatic masses and typical imaging features of pancreatic ductal adenocarcinoma, no preoperative sampling should be carried out and the patients should be referred directly to surgical evaluation (LoE 2b, GoR B).
2- Resectable pancreatic masses with atypical imaging features should be referred to EUS evaluation and EUS-guided sampling (LoE 3b, GoR B).
3- Borderline resectable pancreatic masses candidates for neoadjuvant therapy should be referred to EUS evaluation and EUS-guided sampling (LoE 2b, GoR C).
4- Locally advanced, unresectable solid pancreatic masses in patients who are candidates for cancer therapy should be referred to diagnostic biopsy (LoE 2b, GoR B).
5- Locally advanced, unresectable solid pancreatic masses should be evaluated for US-guided percutaneous biopsy. If percutaneous approach is not feasible, EUS approach should be considered (LoE 5, GoR D).
6- Percutaneous US-guidance should be preferred to CT guidance because of the lower complication rates (LoE 2b, GoR B).
7- Biopsy should be performed on suspected liver metastases, if any, to establish a diagnosis and staging of the disease (LoE 5, GoR D).

8- Tissue sampling of pancreatic cystic masses should be performed under EUS guidance (LoE 5, GoR D).

9- Pancreatic cystic masses with typical imaging features requiring surgical treatment should not be sampled before resection (LoE 5, GoR D).

10- US-guided percutaneous biopsy of a transplanted pancreas must be carried out in a transplant center (LoE 5, GoR D).

**Approval 100%**

- Percutaneous FNA carried out under US guidance is a sensitive, accurate, and safe procedure in the diagnosis and management of solid pancreatic neoplasms. Diagnostic accuracy reported in the literature (98.7%) is based on a high number of cases [28].
- The presence of a cytologist and the use of suction needles permit acquisition of samples of high diagnostic quality, thus reducing the need to repeat FNA [28].

**Approval 100%**

Results obtained in large series reported in the literature reveal that percutaneous FNA of pancreatic masses present a diagnostic accuracy ranging between 75 and 99.4% [28–30]. Considering only FNA carried out under US guidance, a diagnostic accuracy ranging between 91 and 99.4% has been reported with sensitivity ranging between 81 and 99.4% [28–30]. The results of the study carried out by D’Onofrio et al. thus compare favorably with the data reported in the literature in terms of sensitivity and diagnostic accuracy (98.7%), but they are obtained in a larger patient population. Percutaneous FNA performed under US guidance is a sensitive, accurate, and safe procedure in the diagnosis and management of solid pancreatic neoplasms. The data related to the study carried out by D’Onofrio et al. support the use of percutaneous US-guided FNA compared to EUS guidance or biopsy as the first-line tool for invasive characterization of unresectable solid pancreatic lesions. The presence of a cytologist and the use of suction needles permit acquisition of samples of high diagnostic quality, thus reducing the need to repeat FNA [28].

**Acknowledgements** SIUMB experts committee with affiliations: Esterita Accogli: Department of Internal Medicine, Centre of Research and Learning in Ultrasound, Ospedale Maggiore, Bologna, Italy; Fabia Attili: Digestive Disease Center, Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Raffaella Basilico: Department of Neuroscience, Imaging and Clinical Sciences, University “G. d’Annunzio”, Chieti, Italy; Michele Bertolotto: Department of Radiology, University of Trieste, Cattinara Hospital, Trieste, Italy; M. Gabriella Brizi: Department of Emergency Radiology, Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Elisabetta Buscarini: Gastroenterology Unit, ASST Crema, Ospedale Maggiore, Crema, Italy; Corrado Caiazzo: Breast Screening Center, ASL 1 Naples, Italy; Fabrizio Calliada: Institute of Radiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Vito Cantisani: Department of Radiological Sciences, Policlinico Umberto I, University Sapienza, Rome, Italy; Alessandro Carriero: Department of Radiology, University of Novara, Ospedale Maggiore della Carità, Novara, Italy; Alder Casadei: Ultrasound Association of South-Tyrol, Bolzano Health District, Piazza, Bolzano, Italy; Orlando Catalano: Radiology Division, Istituto Diagnostico Varelli, Naples, Italy; Gaspare D’Anneo: Ultrasound Diagnostics Center, Messina, Italy; Marco De Prizio: General Surgery Division, San Donato Hospital, Aрезzo, Italy; Ilario de Sio: Department of Hepato-gastroenterology, Second University of Naples, Naples; Giuliо Di Candidо: Department of General Surgery, Translational and New Technologies in Medicine, University of Pisa, Italy; Mirko D’Onofrio: Department of Radiological Sciences, University of Verona, Italy; Ferdinando Drighi: Institute of Radiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Francesco Maria Drudi: Department of Radiological Sciences, Policlinico Umberto I, University Sapienza, Rome, Italy; Giovanna Ferraioli: Department of Ultrasound in Tropical and Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Giampiero Francia: Interventional and Diagnostic Ultrasound Unit, Pineta Grande Hospital, Castelvolutino, Caserta, Italy; Antonio Granata: Department of Nephrology and Dialysis, Ospedale Cannizzaro, Catania, Italy; Giovanni Iannetti: Unit of Internistic Ultrasound, Department of Medicine and Science of Aging, University “G. d’Annunzio” Chieti, Italy; Giovanni Maconi: Gastroenterology Unit, Department of Biomedical and Clinical Sciences, ASST Fatebenefratelli-Sacco Hospital, University of Milan, Italy; Fabrizio Magnoli: Gastroenterology and Digestive Endoscopy Unit, San Donato Hospital, Arezzo, Italy; Paolella Mirk: Department of Radiology, Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Fabio Piscaglia: Department of Internal Medicine, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; Maurizio Pompili: Department of Gastroenterology, Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Gian Ludovico Rapaccini: Department of Internal Medicine Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Cosimo Schiavone: Unit of Internistic Ultrasound, Department of Medicine and Science of Aging, University “G. d’Annunzio” Chieti, Italy; Luca Maria Sconfienza: Department of Internal Medicine, Interventional Ultrasound Unit, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; Carla Serra: Department of Diagnostic and Interventional Radiology, Istituto Ortopedico Galeazzi, Milan, Italy; Maurizio Soresi: Division of Internal Medicine, Biomedical Department of Internal Medicine and Specialties (Di.Bi.M.I.S.), University of Palermo; Stefania Specia: Department of Radiology, Catholic University of the Sacred Heart- Fondazione Policlinico A. Gemelli, Rome, Italy; Roberto Stramare: Department of Medicine (DIMED), Radiology Division, University of Padua, Italy; Luciano Tarantino: Department of Surgery, Interventional Hepatology Unit, Andrea Tortora Hospital, Padani, Italy; Massimo Valentinò: Department of Radiology, Ospedale Sant’Antonio Abate, Tolimezzo, Udine, Italy; Gianfranco Vallone: Department of Pediatric Radiology, University Hospital Federico II, Naples, Italy; Gianpaolo Vidili: Department of Surgical and Experimental Medical Sciences, Internal Medicine, University of Sassari, Italy.

**Funding** Open access funding provided by Università degli Studi di Verona within the CRUI-CARE Agreement.
Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. D’Onofrio M, Gallotti A, Pozzi MR (2010) Imaging techniques in pancreatic tumors. Expert Rev Med Devices 7(2):257–273
2. Vidili G, De Sio I, D’Onofrio M, Mirk P, Bertolotto M, Schiavone C. SIUMB Experts Committee (2019) SIUMB guidelines and recommendations for the correct use of ultrasound in the management of patients with focal liver disease. J Ultrasound 22(1):41–51
3. Cosgrove D, Piscaglia F, Bamber J et al (2013) EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: clinical applications. Ultrasschall Med 34:238–253
4. Piscaglia F, Nolsoe C, Dietrich CF et al (2012) The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. Ultrasschall Med 33(1):33–59
5. Jønnsen C, Dietrich CF (2009) Endoscopic ultrasound-guided fine-needle aspiration biopsy and trucut biopsy in gastrointestinal—an overview. Best Pract Res Clin Gastroenterol 23:743–759
6. D’Onofrio M, Biagio E, Gerardi C et al (2014) Diagnostic performance of Contrast-Enhanced Ultrasound (CEUS) and Contrast-Enhanced Endoscopic Ultrasound (ECEUS) for the differentiation of pancreatic lesions: a systematic review and meta-analysis. Ultrasschall Med 35(6):515–521
7. Quaia E (2007) Mezzi di contrasto in ecografia. Applicazioni addominali. Springer, New York
8. D’Onofrio M, Zamboni G, Faccioli N et al (2007) Ultrasonography of the pancreas. 4. Contrast-enhanced imaging. Abdom Imaging 32:171–181
9. Schima W, Ba-Salamah A, Köblinger C et al (2007) Pancreatic adenocarcinoma. Eur Radiol 17:638–649
10. Kim JH, Park SH, Yu ES et al (2010) Visually isooattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. Radiology 257:87–96
11. D’Onofrio M, Crosara S, Signorini M et al (2013) Comparison between CT and CEUS in the diagnosis of pancreatic adenocarcinoma. Ultrasschall Med 34(4):377–381
12. Claudon M, Cosgrove D, Albrecht T et al (2008) Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)—update 2008. Ultrasschall Med 29:28–44
13. Martínez-Noguera A, D’Onofrio M (2007) Ultrasoundography of the pancreas. 1. Conventional imaging. Abdom Imaging 32:136–149
14. Nagase M, Furuse J, Ishii H, Yoshino M (2003) Evaluation of contrast enhancement patterns in pancreatic tumors by coded harmonic sonographic imaging with a microbubble contrast agent. J Ultrasound Med 22:789–795
15. D’Onofrio M, Zamboni G, Tognolini A et al (2006) Mass-forming pancreatic: value of contrast-enhanced ultrasound. World J Gastroenterol 12(26):4181–4184
16. Hocke M, Schulze E, Gottschalk P et al (2006) Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatic and pancreatic cancer. World J Gastroenterol 12(2):246–250
17. D’Onofrio M, Barbi E, Dietrich CF et al (2012) Pancreatic multicenter ultrasound study (PAMUS). Eur J Radiol 81:630–638
18. Laghi F, Catalano O, Maresca M, Sandomenico F, Sian A (2010) Indeterminate, subcentimetric focal liver cancers in cancer patients: additional role of contrast-enhanced ultrasound. Ultrasschall Med 31(3):283–288
19. Michl P, Pauls S, Gress TM (2006) Evidence based diagnosis and staging of pancreatic cancer. Best Pract Res Clin Gastroenterol 20(2):227–251
20. Falconi M, Bartsch DK, Eriksson B et al (2012) ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology 95:120–134
21. Malago R, D’Onofrio M, Zamboni GA et al (2009) Contrast-enhanced sonography of nonfunctioning pancreatic neuroendocrine tumors. AJR Am J Roentgenol 192:424–430
22. Hoefel C, Job L, Ladam-Marcus V et al (2009) Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast enhanced ultrasonography. Dig Dis Sci 54:2040–2046
23. Italian Association of Hospital Gastroenterologists and Endoscopists (2014) Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms. Dig Liver Dis 46(6):479–493
24. Rickes S, Mönkemüller K, Malfertheiner P (2006) Echoenhanced ultrasound with pulse inversion imaging: a new imaging modality for the differentiation of cystic pancreatic tumours. World J Gastroenterol 12:2205–2208
25. D’Onofrio M, Megibow AJ, Faccioli N et al (2007) Comparison of contrast-enhanced sonography and MRI in displaying anatomic features of cystic pancreatic masses. AJR 189:1435–1442
26. Sidhu PS, Cantisani V, Dietrich CF et al (2017) The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in non-hepatic applications: update 2017 (long version). Ultrasschall Med 39(2):e2–e44
27. Sidhu PS, Brabrand K, Cantisani V et al (2015) EFSUMB Guidelines on interventional ultrasound (INVUS), part II. Diagnostic ultrasound-guided interventional procedures (long version). Ultrasschall Med 36:E15–E35
28. D’Onofrio M, De Robertis M, Barbi E et al (2015) Ultrasound-guided percutaneous fine-needle aspiration of solid pancreatic neoplasms: 10-year experience with more than 2000 cases and a review of the literature. Eur Radiol 26(6):1801–1807
29. Bhatia P, Srinivasan R, Rajwanshi A et al (2008) 5-year review and reappraisal of ultrasound-guided percutaneous transabdominal fine needle aspiration of pancreatic lesions. Acta Cytol 52:523–529
30. Garre Sanchez MC, Rendon Unceta P, Lopez Cano A et al (2007) Ultrasound-guided biopsy of the pancreas: a multicenter study. Rev Esp Enferm Dig 99:520–524

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.