Original paper

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Contrast-Enhanced Ultrasound for differential diagnosis of pancreatic mass lesions: a meta-analysis.

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Abstract

Aim: To evaluate the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) as a method for diagnosing pancreatic lesions with regard to the ductal pancreatic carcinoma and the differentiation of neoplastic from non-neoplastic lesions. **Material and methods:** Relevant studies published by September 6, 2015 were retrieved from PubMed, Embase, and Cochrane Central Trials databases. The articles included were mainly based on the following criteria: use of CEUS as the diagnostic tool, and the use of histology as the reference method. Two independent reviewers inspected all these papers to confirm the matching of the inclusion criteria. One reviewer with methodological expertise extracted the data from the included studies. Sensitivity, specificity and diagnostic odds ratio (DOR) were used to obtain overall estimates. **Results:** Eighteen studies out of 734 articles initially identified met the inclusion criteria. The primary study objective with respect to ductal adenocarcinoma was verified in 15 studies. The pooled estimate of CEUS sensitivity for the differential diagnosis of duct adenocarcinomas was 0.90 (95 % CI, 0.89–0.92), and the specificity was 0.88 (0.84-0.90). The pooled estimate for DOR was 56.38 (29.91-106.33). The area under the curve under the summary receiver operating characteristic (SROC) was 0.95. 12 out of 18 studies examined CEUS sensitivity and the average specificity with regard to the secondary study objective, distinguishing between neoplastic lesions and non-neoplastic lesions, were 0.95 (0.94-0.96) and 0.83 (0.77–0.87). The pooled estimate for DOR was 73.25(45.31-118.43). The area under the SROC curve was 0.96. **Conclusions:** CEUS is a promising, reliable modality for the differential diagnosis of pancreatic adenocarcinoma in patients with pancreatic mass lesions. The presence of a hypoenhanced lesion was a sensitive predictor of pancreatic adenocarcinomas. It seems to be a useful tool in clinical practice.

Keywords: contrast-enhanced ultrasound (CEUS), pancreatic carcinoma, pancreatic neoplastic lesion

Introduction

Contrast-enhanced ultrasound (CEUS) of the pancreas has led to great development in the diagnostic capabilities of conventional ultrasound (US) which is usually applied in the initial evaluation of pancreatic diseases. When a pancreatic lesion has been detected, an immediate differential diagnosis is essential to proceed to an appropriate management. Moreover, the detection of an incidental pancreatic lesion at US is a relatively frequent clinical scenario. Ultrasonography is well-known to be the noninvasive imaging modality chosen for the first evaluation of the pancreas. In addition, during the US study, the administration of microbubble contrast media is reported to improve pancreatic solid and cystic lesion characterization. The contrast-enhanced phase is observed after the injection of a intravascular contrast media and the pancreatic tumor vascularization is visible by CEUS. With the help of harmonic microbubble-specific software, the contrast media produces a hyper echoic signal in the regions where the vessels are present, and the non-vascularized tissue remains non-enhancing, thus making a differential diagnosis possible [1-4].

In 2008, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) first included pancreatic applications of CEUS in its guidelines [5]. The role of CEUS for pancreatic evaluation was then underlined in the 2011 EFSUMB guidelines [6], in which the first recommendation was the characterization of ductal adenocarcinoma (recommendation level: A-1b).

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Among the recommendations, the differentiation between pseudocysts and cystic tumors was recommended as level A for the application of CEUS, and the distinction between solid and cystic lesions providing information for the choice of the subsequent imaging modality (i.e. MRI and/or endoscopic US for cystic lesions), resulting in a better management of patients.

With the development of CEUS, a series of well-designed prospective and retrospective studies have been assessed for differentiating pancreatic masses lesions, with the sensitivity ranging from 73% to 100% and specificity ranging from 50% to 100% [3]. Therefore, the main objective of the present study was to perform a meta-analysis of published information to assess the real diagnostic value of pancreatic diseases and its application in the clinical practice.

Research methods

Types of studies

All published articles relevant to CEUS were retrieved from PubMed, Embase, and Cochrane Central Trials databases. The search terms were ("contrast enhanced or contrast enhancement or echo enhanced or contrast imaging"), (ultrasonography or ultrasound or ultrasonography) and (Sonovue or Levovist) with the limit date as September 6, 2015 to identify potentially eligible studies. All references of the retrieved articles were scrutinized to identify any additional articles had not been missed by the former search; if an article had been missed, the search strategy was checked and the search was redone..

Two independent reviewers inspected the retrieved studies to identify those that conformed with the inclusion criteria. Where disagreement occurred, attempts were made to resolve this through discussions after the studies were scrutinized. Contingency numbers of true positives (TPs), false positives (FPs), false negatives (FNs), and true negatives (TNs) were obtained from data to calculate sensitivity and/or specificity. One reviewer with methodological competence independently extracted the data from the included studies. Any disagreements were resolved by discussion and, if any clarification was necessary, the authors of these studies were contacted.

Study selection

The inclusion criteria were as follows: 1) the performance imaging method was CEUS in pancreatic diseases and Sonovue or Levovist was the contrast agent used; 2) evaluation by diagnostic clinical trials of the accuracy of CEUS for the differential diagnosis of pancreatic solid masses; 3) use of surgical specimen, positive cytological finding, or core biopsy as the diagnosis reference standard, or a follow-up period of at least 6 months; 4) data were available to construct tables for true-positive, false-positive, false-negative, and true-negative determinations; 5) articles were English; and 6) outcome measurement were consistent.

The exclusion criteria were the following: 1) without evaluation of solid lesions of the pancreas; 2) lack of useful data for the analysis (no enhancement patterns reported for the diagnosis, therefore sensitivity and specificity could not be obtained); 3) overlap with the selected studies (ie, studies from the same study group, institution, and period of inclusion); 4) reviews, editorials, case reports, and corresponding letters that did not report their own data; and 5) studies were not suitable for the reference standard.

Statistical methods

Meta-analysis was performed for the diagnostic accuracy of CEUS by calculating pooled estimates of sensitivity, specificity, and diagnostic odds ratio (DOR) across the studies. Pooling results (included corresponding 95% confidence intervals [CIs]) were conducted by using the fixed effect model (Mantel-Haenszel method) when significant heterogeneity was not present; the random-effects model (DerSimonian-Laird method) was applied in which the weights were the inverse of variance of each single study. The pooled results sensitivity, specificity, and SROC curve were conducted by using Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Ramony Cajal Hospital, Madrid Spain). The Cochrane Q test was used to detect the heterogeneity among studies. When the p values were <0.10 it indicated the presence of heterogeneity. With regard to inconsistency (I^2), the percentage of the variability attributable to heterogeneity, >50% was considered significant. [7-10].

The pooled DORs were obtained calculating the weighted average using the DerSimonian Laird random effect model. The DORs combined sensitivity and specificity into one measure of diagnostic performance. The value of a DOR equal to 1 meant the method had no ability to discriminate, while the higher the DOR, the better the ability of the test to differentiate subjects with and without the disease of interest.

The summary receiver-operating characteristic (SROC) curve was constructed by using the Moses-Shapiro-Littenberg method to summarize the difference from each study. In addition, the area under the curve (AUC) was calculated, the value ranging from 0.5 to 1.0, when the value closed to 0.5 indicated a poor test while a value of 1.0 indicated a perfect test.

Before performing the statistic analysis , the quality of eligible studies was evaluated with the Quality Assessment of Diagnostic Studies (QUADAS), a tool specially designed for the studies on diagnostic accuracy: the items of QUADA were quantified with "yes", "no", or "unclear" [11].

Results

Eligible studies and quality assessment

The records identified through Pubmed, Embase and Cochrane databases were 734; after screening of the records, 18 studies fulfilled our eligibility criteria. The process of study selection is shown in fig 1. Data for evaluating the accuracy of CEUS for the differential diagnosis of pancreatic lesions were extracted from these studies. The quality of the eligible studies, assessed according to the QUADAS criteria, is reported in fig 2.

Study characteristics

The main characteristics of the studies included in the analysis are reported in Table I. Thirteen studies were on the subject of diagnosis [12-17,20-21,23-25,27-30,32-33] and 5 studies were concerned with suspicion in the clinical setting [18-19,22,26,31]. In these studies 2704 patients were enrolled while 2664 were included in the analysis. Nine studies had a prospective design. Sonovue was used in 12 studies (67%) and 6 used the Levovist.

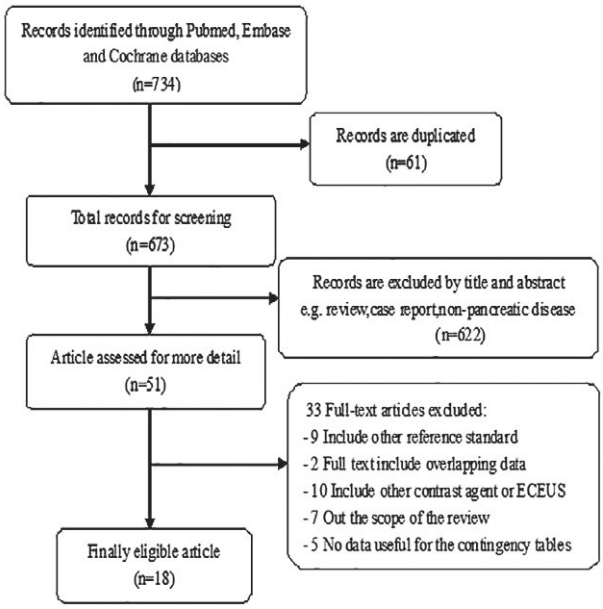


Fig 1. Flowchart of the literature search and selection

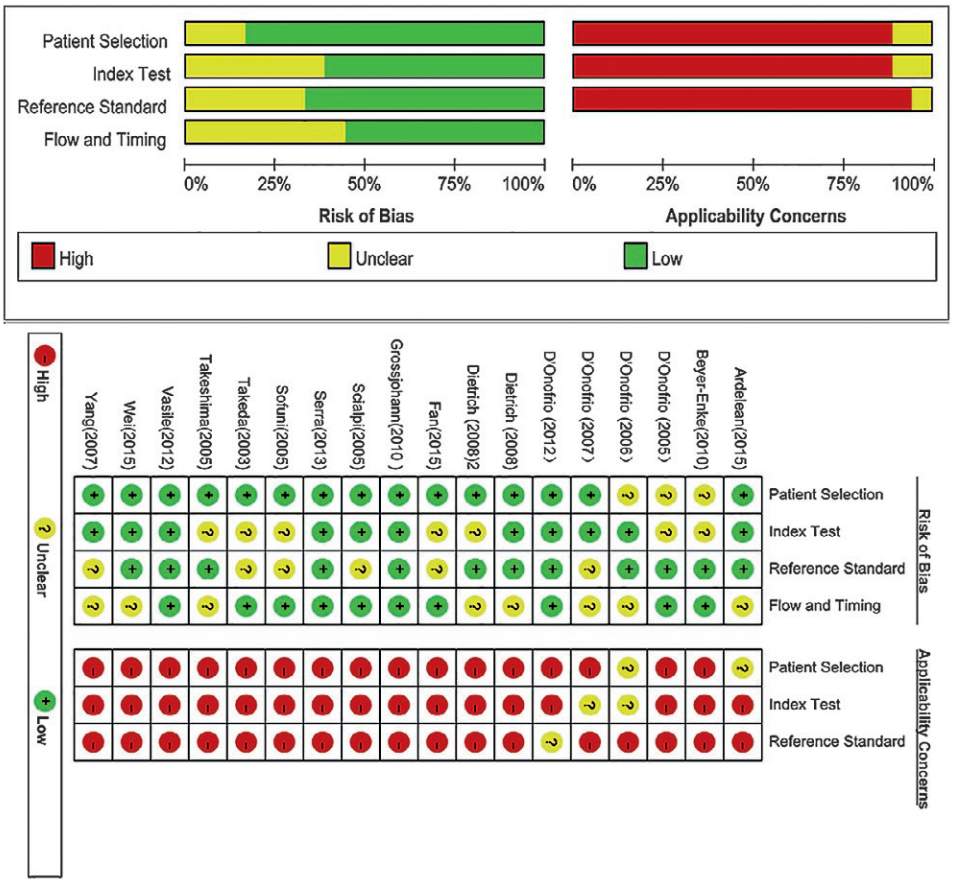


Fig 2. The quality of the eligible studies as assessed according to the Quality Assessment of Diagnostic Accuracy Studies criteria.

Table I. Baseline characteristics of studies included in the meta-analysis

Study	Contrast agent	Setting	N enrolled	N analyzed	Sex (%male)	Age (mean, y)	Center	Design
D'Onofrio(2005)	Sonovue	On diagn	42	42	uk	uk	Mono	Prosp
D'Onofrio(2006)	Sonovue	On diagn	173	173	60.1	59.7	Mono	Retrosp
D'Onofrio(2007)	Sonovue	On diagn	33	33	45.5	50.9	Mono	Retrosp
D'Onofrio(2012)	Sonovue	On diagn	1439	1439	54.8	61.3	Multi	Retrosp
Dietrich(2008)	Levovist	On diagn	93	93	uk	uk	Multi	Prosp
Dietrich(2008)	Sonovue	On diagn	112	112	49	57.9	Multi	Prosp
Beyer-Enke(2010)	Sonovue	On susp	127	114	55.3	62.0	Mono	Prosp
Grossjohann(2010)	Sonovue	On susp	49	49	46.9	66.0	Mono	Prosp
Sofuni(2005)	Levovist	On diagn	50	50	uk	uk	Mono	Not spec
Scialpi(2005)	Levovist	On susp	26	26	50.0	56.8	Multi	Prosp
Serra(2013)	Sonovue	On diagn	144	127	59.8	67.2	Mono	Prosp
Takeda(2003)	Levovist	On diagn	37	37	uk	uk	Mono	Prosp
Takeshima(2005)	Levovist	On diagn	34	34	61.8	66.6	Mono	Not spec
Vasile(2012)	Levovist	On susp	76	76	50.0	59.5	Mono	Prosp
Ardelean(2015)	Sonovue	On diagn	91	83	uk	uk	Mono	Retrosp
Fan(2015)	Sonovue	On susp	64	64	48.8	52.4	Mono	Retrosp
Wei(2015)	Sonovue	On diagn	53	51	54.9	56.1	Mono	Retrosp
Yang(2007)	Sonovue	On diagn	61	61	45.9	54.9	Mono	Retrosp

N – number of patients, Uk – unknown, y – years; Prosp – prospective, Retrosp – retrospective, Not spec – not specified, Mono – mono-center, Multi – multicenter, On diagn – on diagnosis, On susp – on suspicion.

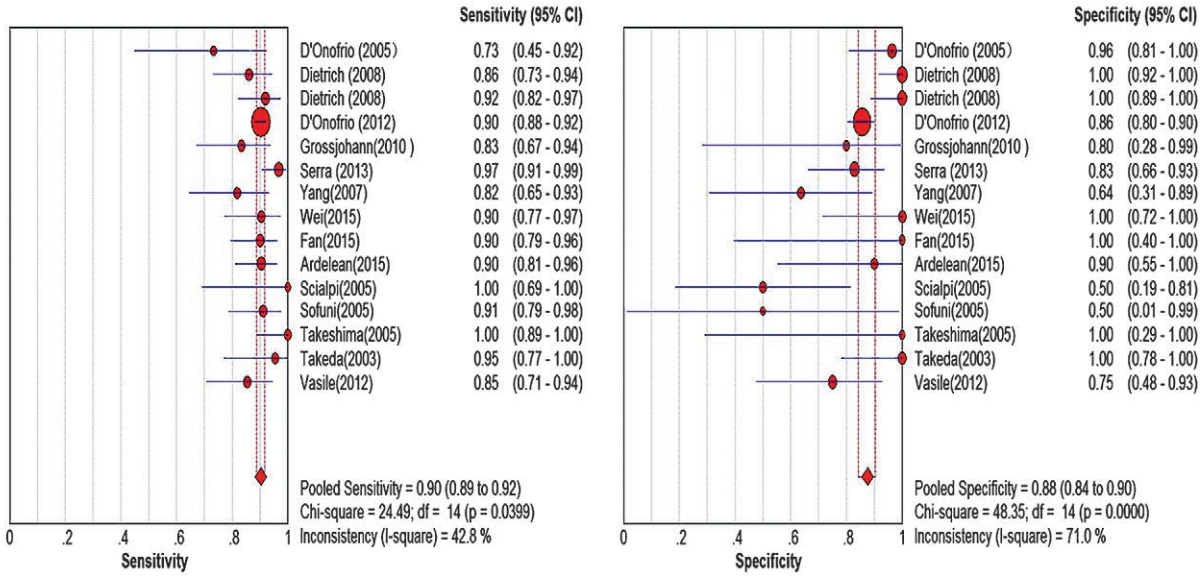


Fig 3. Forest plot of the meta-analysis of sensitivity (left) and specificity (right) for the differentiation of pancreatic duct adenocarcinoma.

Assessment of CEUS performance in pancreatic ductal adenocarcinomas characterization

The pooled estimate of CEUS sensitivity in the differential diagnosis of pancreatic adenocarcinomas and other pancreatic focal masses (random-effects model) was 0.90 (95 % CI, 0.89–0.92). The pooled specificity (random-effect model) was 0.88 (95 % CI, 0.83-0.89). Significant heterogeneity was found in the sensitivity (Cochran Q test = 24.49, degrees of freedom [df] =14, p=0.0399, I^2=42.8%) and specificity (Cochran Q test =48.35, degrees of freedom [df] =14, p=0.0005, I^2=63.3%) (fig 3). The AUC under the SROC was 0.9488 (fig 4).

The Pooled estimate of DOR was 56.38 (95%CI, 29.91-106.33).

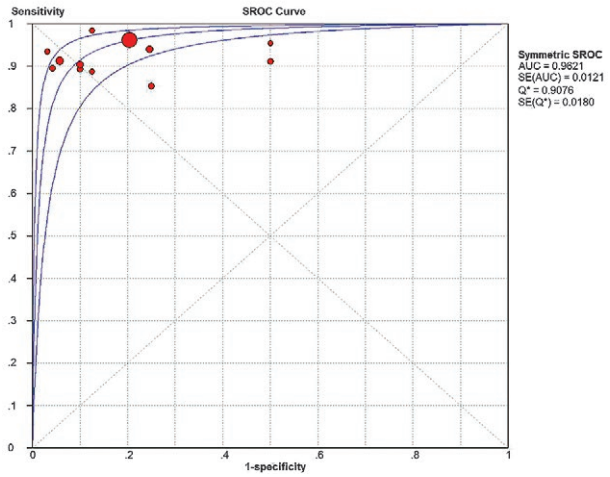


Fig 4. The summary receiver operating characteristic (SROC) curve, used for differentiation of pancreatic duct adenocarcinoma. SROC- summary receiver operating characteristic; AUC- area under the curve; Q*- the point at which sensitivity and specificity are equal.

Table II. Results of sensitivity, specificity and diagnostic odds ratio

	AC vs nonAC		NP vs nonNP	
	N	95%CI	N	95%CI
Sensitivity	15	0.90(0.89-0.92)	10	0.95(0.94-0.96)
Specificity	15	0.88(0.84-0.90)	10	0.83(0.77-0.87)
DOR	15	56.38(29.91-106.33)	10	73.25(45.31-118.43)

AC – adenocarcinomas, NP – neoplastic. N – number of studies, DOR – diagnostic odds ratio

Assessment of CEUS performance in differentiating between neoplastic and non-neoplastic pancreatic lesions

The pooled sensitivity and specificity were 0.95 (95%CI, 0.94-0.96) and 0.83 (95%CI, 0.77-0.87) from 12 studies. The forest plot in fig 5 shows the sensitivity and specificity of each study with respect to the objective analysis. The pooled estimate of DOR was 73.25 (95%CI, 45.31-118.43). The AUC under the SROC was 0.96 (fig 6).

The Pooled estimates of sensitivity, specificity and DOR are shown in Table II.

Discussions

CEUS was confirmed as a valid imaging modality for the assessment of pancreatic lesions. Compared with other imaging techniques, the advantage of CEUS is the capability to obtain a real-time observation of blood perfusion of the lesion. Due to the fixed time of scanning, CE-CT/MRI has no ability to capture a transient enhancement [2,14]. CEUS represents a feasible and safe technique to immediately characterize and stage the disease. When a pancreatic tumor has been detected, an immediate and correct differential diagnosis is mandatory to direct appropriate management. This meta-analysis evaluated the capability of CEUS to detect and characterize pancreatic diseases and its possible use in the clinical routine, summarizing the value of CEUS in the diagnosis of pancreatic lesions.

Our primary objective was to evaluate the power of CEUS in characterizing pancreatic ductal adenocarcinoma. As is known from a Pancreatic Multicenter Ultrasound Study (PAMUS), ductal adenocarcinomas are typically hypovascular and with a hypoenhanced mass due to the prominent desmoplasia and fibrosis, and if the typical hypoenhanced pattern of ductal adenocarcinoma is not present, another diagnosis has to be made, such as neuroendocrine lesion and metastases [1,2,33]. In this meta-analysis, the overall sensitivity 0.90 (95 % CI 0.89 – 0.92), overall specificity 0.88 (95 % CI 0.84 – 0.90), and DOR of 56.39 (95 % CI 29.91-106.33) demonstrated an excellent capability of CEUS for the differential diagnosis in the solid pancreatic masses, thus providing a rapid assessment of the pancreas for further management.

Since the US examination is the preferred first-line diagnostic imaging modality, suspicious lesions can be detected at the first US evaluation. In the present meta-analysis CEUS evidenced a high accuracy, being important especially in tumors with uncertain hypervascularity or in doubtful septa enhancement lesions. When a pancreatic mass is detected, the CEUS exam must be performed in the same session with grey scale/Doppler US examination.

The secondary objective in this meta-analysis was to differentiate between neoplastic and non-neoplastic pancreatic lesions. In fact, in clinical practice when a pancreatic mass is detected, the first steps are toward the differential diagnosis between neoplastic vs. non-neoplastic and solid vs. cystic lesions. In this meta-analysis, the CEUS proved also to be a reliable method in characterizing the nature of neoplastic vs. non-neoplastic lesions, demonstrated by an overall sensitivity of 0.95 (95 % CI 0.94 – 0.96), specificity of 0.83 (95 % CI 0.77 – 0.87) and DOR of 73.25 (95 % CI 45.31 – 118.43). CEUS improves the differential diagnosis due to a technical feature of accurately describing the enhancement of septa, nodules, and demonstrated a good ability in the pathological correlation of cystic pancreatic lesions [12].

This meta-analysis was based on observational studies, two different clinical settings (on suspicion, on diagnosis) and two different experimental designs (retrospective, prospective) to summarize the available

evidence of the role of CEUS for the differential diagnosis of pancreatic adenocarcinoma. With regard to the literature quality, many articles did not have sufficient information, and the QUADS item had to be evaluated as "unclear" because it was difficult to exclude the presence of biases that could influence the study results. In addition, in this paper, the publication bias cannot be excluded, although the analysis of the funnel plot indicated it should be small.

In conclusion, due to the obtained results and to their noninvasive characteristics, CEUS is a promising reliable modality for the early characterization in patients with pancreatic lesions. Due to the specific features obtained during CEUS examination, the method ensures the completion of diagnosis for pancreatic mass lesions; it appears to be a useful tool in clinical practice.

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Conflict of interest: none

References

1. Rickes S, Rauh P, Uhle C, Ensberg D, Mönkemüller K, Malfertheiner P. Contrast-enhanced sonography in pancreatic diseases. Eur J Radiol 2007; 64: 183-188.
2. Rickes S, Monkemuller K, Malfertheiner P. Contrast-enhanced ultrasound in the diagnosis of pancreatic tumors. JOP 2006; 7: 584-592.
3. D'Onofrio M, Biagioli E, Gerardi C, et al. 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. Ultraschall Med 2014; 35: 515–521.
4. Yan K, Dai Y, Wang YB, et al. The role of contrast-enhanced ultrasound in diagnosing pancreatic diseases. Chin J Ultrasononogr 2006; 15: 361-364.
5. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)-update 2008. Ultraschall Med 2008; 29: 28-44.
6. Piscaglia F, Nolsoe C, Dietrich CF, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med 2012; 33: 33–59.
7. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
8. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143: 29-36.
9. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993; 12: 1293-1316.
10. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat Med 2002; 21: 1525-1537.
11. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003; 3: 25.
12. D'Onofrio M, Malago R, Zamboni G, et al. Contrast-enhanced ultrasonography better identifies pancreatic tumor vascularization than helical CT. Pancreatology 2005; 5: 398-402.
13. D'Onofrio M, Zamboni G, Tognolini A, et al. Mass-forming pancreatitis: value of contrast-enhanced ultrasonography. World J Gastroenterol 2006; 12: 4181-4184.
14. D'Onofrio M, Megibow AJ, Faccioli N, et al. Comparison of contrast-enhanced sonography and MRI in displaying anatomic features of cystic pancreatic masses. AJR Am J Roentgenol 2007; 189: 1435-1442.
15. D'Onofrio M, Barbi E, Dietrich CF, et al. Pancreatic multicenter ultrasound study (PAMUS). Eur J Radiol 2012; 81: 630-638.
16. Dietrich CF, Braden B, Hocke M, Ott M, Ignee A. Improved characterisation of solitary solid pancreatic tumours using contrast enhanced transabdominal ultrasound. J Cancer Res Clin Oncol 2008; 134: 635-643.
17. Dietrich CF, Ignee A, Braden B, Barreiros AP, Ott M, Hocke M. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. Clin Gastroenterol Hepatol 2008; 6: 590-597.
18. Beyer-Enke SA, Hocke M, Ignee A, Braden B, Dietrich CF. Contrast enhanced transabdominal ultrasound in the characterisation of pancreatic lesions with cystic appearance. JOP 2010; 11: 427-433.
19. Grossjohann HS, Rappeport ED, Jensen C, et al. Usefulness of contrast-enhanced transabdominal ultrasound for tumor classification and tumor staging in the pancreatic head. Scand J Gastroenterol 2010; 45: 917-924.
20. Sofuni A, Iijima H, Moriyasu F, et al. Differential diagnosis of pancreatic tumors using ultrasound contrast imaging. J Gastroenterol 2005; 40: 518-525.
21. Dorffel Y, Wermke W. Neuroendocrine tumors: characterization with contrast-enhanced ultrasonography. Ultraschall Med 2008; 29: 506-514.
22. Scialpi M, Midiri M, Bartolotta TV, et al. Pancreatic carcinoma versus chronic focal pancreatitis: contrast-enhanced power Doppler ultrasonography findings. Abdom Imaging 2005; 30: 222-227.
23. Serra C, Felicani C, Mazzotta E, et al. Contrast-enhanced ultrasound in the differential diagnosis of exocrine versus neuroendocrine pancreatic tumors. Pancreas 2013; 42: 871-877.
24. Takeda K, Goto H, Hirooka Y, et al. Contrast-enhanced transabdominal ultrasonography in the diagnosis of pancreatic mass lesions. Acta Radiol 2003; 44: 103-106.
25. Takeshima K, Kumada T, Toyoda H, et al. Comparison of IV contrast-enhanced sonography and histopathology of pancreatic cancer. AJR Am J Roentgenol 2005; 185: 1193-1200.

26. Vasile TA, Feier D, Socaciu M, et al. Contrast enhanced ultrasound and computer tomography diagnosis of solid and mixed pancreatic tumors–analysis of confounders. J Gastrointestin Liver Dis 2012; 21: 285-292.
27. Ardelean M, Sirli R, Sporea I, et al. The value of contrast-enhanced ultrasound in the characterization of vascular pattern of solid pancreatic lesions. Med Ultrason 2015; 17: 16-21.
28. Fan Z, Yan K, Wang Y, et al. Application of contrast-enhanced ultrasound in cystic pancreatic lesions using a simplified classification diagnostic criterion. Bio Med Res Int 2015; 2015: 974621.
29. Wei Y, Yu XL, Liang P, et al. Guiding and controlling percutaneous pancreas biopsies with contrast-enhanced ultrasound: target lesions are not localized on B-mode ultrasound. Ultrasound Med Biol 2015; 41: 1561-1569.
30. Yang W, Chen MH, Yan K, Wu W, Dai Y, Zhang H. Differential diagnosis of non-functional islet cell tumor and pancreatic carcinomawith sonography. Eur J Radiol 2007; 62: 342-351.
31. Fan Z, Li Y, Yan K, et al. Application of contrast enhanced ultrasound in the diagnosis of solid pancreatic lesions- a comparison of conventional ultrasound and contrast-enhanced CT. Eur J Radiol 2013; 82: 1385-1390.
32. Rickes S, Rauh P, Uhle C, Ensberg D, Mönkemüller K, Malfertheiner P. Contrast-enhanced sonography in pancreatic diseases. Eur J Radiol 2007; 64: 183-188.
33. Martinez-Noguera A, D'Onofrio M. Ultrasonography of the pancreas. 1. Conventional imaging. Abdom Imaging 2007; 32: 136-149.