Liver contrast-enhanced ultrasound improves detection of liver metastases in patients with pancreatic or periampullary cancer

Pavel Taimr, Vivian L. Jongerius, Chulja J. Pek, Nanda C. Krak, Bettina E. Hansen, Harry L. A. Janssen, Herold J. Metselaar, Casper H. J. van Eijck

Ultrasound in Medicine and Biology 2015

ABSTRACT

The aim of this study is to provide a diagnostic performance evaluation of contrast-enhanced ultrasonography (CEUS) in detecting liver metastases in patients with suspected of pancreatic or periampullary cancer. Computed tomography (CT) is often insufficient for detection of liver metastases, but their presence plays a crucial role in the choice of therapy. Eighty-nine patients with suspected pancreatic or periampullary cancer were included in this prospective study with retrospective analysis. Patients underwent an abdominal CT and CEUS. Fifteen patients had liver metastases. The CT sensitivity was 73.3% (11/15), the specificity 93.2% (69/74), the positive predictive value (PPV) 68.8% (11/16) and the negative predictive value (NPV) 94.6% (69/73). Based on CEUS, the sensitivity was 80% (12/15), specificity 98.6% (73/74), PPV 92.3% (12/13) and NPV 96.1% (73/76). CEUS improved characterization of liver lesions in patients with suspected pancreatic or periampullary cancer compared with CT. CEUS can better detect benign liver lesions and distinguish false-positive or indeterminate CT results.

INTRODUCTION

Pancreatic adenocarcinoma is one of the deadliest types of cancer. The overall US mortality rate for cancer has declined by 20% since 1991, according to the [1]. In contrast to many other malignancies, pancreatic cancer is a grim exception, and its death rate is slowly increasing. For all stages combined, the 5-y relative survival rate is only 6%, and most patients will die within the first year of diagnosis. In particular, pancreatic cancer metastasizes frequently, particularly to the liver. Complete surgical resection combined with adjuvant chemotherapy is currently the only potentially curative treatment. The 5-y overall survival in patients undergoing pancreatectomy is 15% – 25% compared to 5% without surgical treatment [2]. However, after a tumor is diagnosed, surgery is an option in only 15% – 20% of all patients. Most tumors are diagnosed at an already non-resectable stage due to late detection and early metastases, particularly in the liver [3-4].

Surgery will not improve survival if metastases are present in the liver. The presence or absence of liver metastases plays a pivotal role in the choice of therapy. It is therefore crucial to have accurate pre-operative methods for the detection of liver metastases [5].

Computed tomography (CT) is currently the reference method for the detection of metastases and is used in combination with clinical and histologic data. Patients suspected of having pancreatic cancer generally receive only an abdominal CT as a first-line investigation. The CT scan has two objectives: evaluation of the tumor's local resectability and exclusion of distant metastases. Although the quality of the CT scan has improved in recent years, the sensitivity for the detection of liver metastases is suboptimal and ranges from 38% to 73% [6-8]. A CT scan alone is often not enough for the detection of metastases, and surgeons frequently encounter metastatic liver lesions during an explorative laparotomy; metastases smaller than 1 cm can be frequently missed.

CT-related radiation exposure should also be taken into account. Magnetic resonance imaging (MRI) is another method for identifying liver metastases, but MRI is usually not part of the routine screening protocol. Despite advances in modern imaging techniques, assessing the presence of liver metastases remains challenging.

Contrast-enhanced ultrasonography (CEUS) is an evolving technology that has been developed over the last decade. With this type of ultrasonography, it is possible to better characterize focal liver lesions [9]. CEUS has repeatedly shown to have high accuracy in diagnosing liver tumors [10-12] and can differentiate between benign and malignant focal liver lesions with a diagnostic accuracy of approximately 87% and a lesion type accuracy of approximately 78% [13-14]. Several limitations of CEUS do exist: The method can be performed only for a short period of time, usually

3–5 min, is operator dependent and the examination may be challenging in obese patients [15]. Usually only one lesion can be evaluated during each contrast-agent-usage period (unless multiple lesions are located in the same segment), but examination can be repeated to evaluate other lesions. Still, CEUS is flexible, inexpensive, lacks radiation risk and is suitable for use in patients with renal insufficiency or allergies to CT contrast agents.

Thus far no study has evaluated the performance of CEUS in assessing liver metastases of patients with suspected pancreatic or periampullary tumors. The aim of this study was to evaluate the diagnostic value of screening CEUS compared to CT scan in the detection of liver metastases in patients suspected of having pancreatic or periampullary cancer.

MATERIAL AND METHODS

Study design

In this single-center, prospective study with retrospective analysis, CEUS was compared to contrast-enhanced CT for the detection of liver metastases. The results of other diagnostic tests, such as MRI, biopsy, laparoscopy or open surgery, as well the outcome of clinical follow-up, were used to define the final diagnosis. In cases where no metastases were observed during surgery or by biopsy, there was a follow-up period consisting of a CT scan at least 3 mo after surgery.

Patients

Between March 2008 and September 2011, 111 patients were enrolled. The inclusion criteria were presence of suspected pancreatic or periampullary cancer. The exclusion criteria were an age <18 y, concomitant serious illness (ie. recent cardiac infarct) and known hypersensitivity to contrast agents to preclude CT or CEUS scanning. All patients were assessed for possible liver metastases. Informed consent from study participants was signed. The procedures were conducted according the ethical standards of the Committee on Human Experimentation of the institution and with the ethical standards of the Helsinki Declaration of 1975.

Methods and procedures

CEUS.

Ultrasonography was performed by various sonographers, but all examinations' cineloops were reviewed by one examiner (PT) with more than 20 y of experience in liver ultrasound and more than 8 y of experience in CEUS. The sonographers were blinded to the patient's pre-existing CT results, but were informed about suspected pancreatic neoplasm and the need to exclude possible liver metastases. CEUS was performed using the Hitachi 900 and Hitachi Preirus ultrasound platforms (Hitachi Medical Systems, Japan) with real-time grayscale, contrast-tuned imaging and a 2.5–5.0 MHz probe. The contrast agent used was SonoVue (Bracco, Italy; range 1.5–2.4 mL; repeated if needed and flushed by isotonic saline). Ultrasound examination was performed in a standardized fashion. First, all patients underwent unenhanced abdominal and hepatic sonography using the fundamental color/power Doppler techniques, and the location, number, size and sonographic features of the focal liver lesions were recorded. CEUS was performed during the hepatic arterial, portal venous and late parenchymal phases, according to the standardized EFSUMB protocol [16]. The vascularity and pattern of enhancement of the lesion compared with the adjacent liver parenchyma were evaluated for diagnosis by CEUS for up to 4 min after the application of the contrast agent. If multiple suspected lesions (more than 8–10) were found, for the arterial phase only the dominant lesion was selected. If one or two lesions were found, then all were checked in the arterial phase. In one case, all three suspected metastases were located close together in adjacent segments and only one arterial phase was performed, but all lesions checked. Still images and digital cineloops were saved and reviewed.

CT scan.

Patients analyzed at Erasmus MC were scanned with a Siemens helical multi-detector CT scanner according to the local triple-phase pancreatic cancer protocol [17], which included noncontrast-enhanced and contrast-enhanced scans in the pancreatic phase after 40 s (2.5- to 3-mm slices) and in the portal phase after 80 s (3–5-mm slices). CT scans performed at other hospitals included triple phase, biphasic (arterial or pancreatic phase and venous phase) or single phase (venous phase) protocols, with 3–5-mm slices.

All scans were evaluated or reassessed (in case of a CT scan from another hospital) by several abdominal radiologists as part of the normal pre-operative clinical workup. Radiologists were aware of all relevant clinical information and made a standard radiology report regarding the tumor's local resectability and the presence or absence of distant metastases.

For the purpose of this study, only the scans of 18 patients suspected of having liver metastases on either CT or CEUS were re-reviewed by a single radiologist (NK) with 5 y dedicated experience in abdominal radiology.

Final reference diagnosis. The final reference diagnosis was obtained by surgery and/or histology plus all available clinical information. Biopsies were taken before or during laparoscopy when suspected metastases were observed. The blood results, such as CEA and CA19-9, as well as size and compartment of the lesions, were assessed, but did not contribute to the final evaluation in this study.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois). Sensitivity, specificity and kappa (overall agreement) were calculated for the detection of metastases. Comparisons between groups were performed using the McNemar test. Further logistic regression was applied to compare CT and CEUS as predictors of metastases.

RESULTS

Study population

For the purposes of the study, 111 patients were enrolled. All patients were suspected of having pancreatic or periampullary cancer. Over the course of the study, 14 patients were excluded. Six patients were excluded because they had only undergone an MRI and not a CT scan, and eight patients were excluded because their CT and/or CEUS scans were not performed according to protocol (most frequently, an overly long time interval elapsed between CEUS and CT). Another eight patients were excluded from analysis because their final diagnosis turned out not to be a pancreatic or periampullary adenocarcinoma (autoimmune pancreatitis in three patients, neuroendocrine tumor in two patients, intra-ductal papillary mucinous neoplasm in two patients and pancreatic cyst in one patient).

The total study population consisted of 89 patients, comprising 55 men and 34 women. The age range was 31–87 y. Pancreas head adenocarcinoma was diagnosed in 66 (74.1%) patients, periampullary adenocarcinoma in 21 (23.9%) patients and 2 (2.2%) patients had adenocarcinoma in the pancreas tail.

CEUS was performed before or after CT; mean interval between CT and CEUS was 27 d (range 0–73). We do not consider the mean interval too long, but there are no reliable guidelines to follow and our patients were treated according to current clinical practice in a tertiary center.

The patients presented with various indications and symptoms. The main symptom was obstructive jaundice (32/89, 35.9%). Furthermore, certain patients presented with symptoms of weight loss, pain, feelings of malaise and gastric outlet obstruction. In three patients, pancreatic carcinoma was discovered during other diagnostic investigations. In seven patients, the main symptom was not clear or non-specific.

In 15 (16.9%) patients, at least one liver metastasis was diagnosed during the diagnostic procedures, at laparotomy or during follow-up.

No adverse events were reported, and no patients with ultrasound or CT contrast agent allergy were encountered.

Computer tomography (CT)

In 40 (44.9%) patients, various focal lesions were observed by CT, and 16 (17.9%) patients were suspected of having liver metastases. In 24 (26.9%) patients, other focal lesions were visualized but were not suspected for metastatic disease. Forty-nine (55%) patients had no focal lesions observed on CT. These results are summarized in Table 1. Furthermore, in two (4.1%) patients with no suspected lesions, fatty liver (steatosis) was present, and in one (2%) patient, calcification of the liver was seen on CT.

Of the 16 patients who were suspected of having liver metastases based on the CT scan, 11 had histologically proven metastases. Therefore, the positive predictive value (PPV) for the detection of liver metastases with CT was 68.8%. A false-positive diagnosis of metastasis was given in five patients (average 11 mm, range 8–15 mm). These lesions were finally diagnosed as cysts (n = 2) or non-specific lesions that could not be characterized further on CT (n = 3). Of the three non-specific lesions, one was due to suboptimal CT quality (5-mm slices, only venous phase), one was a hypervascular lesion to be determined as a shunt on MRI and one involved focal bile duct dilation as shown by CEUS.

In four patients with proven metastasis, non-malignant focal lesions were seen on CT (one patient had 19-mm metastasis and three patients multiple small ones).

Seventy-three patients were not suspected of having liver metastases based on CT. In total, 69 of these patients had no liver metastases. Therefore the negative predictive value for the detection of liver metastases by CT was 94.6%.

The sensitivity of CT in the diagnosis of metastasis in a patients suspected of malignant pancreatic tumor was 73.3% (11/15), its specificity was 93.2% (69/74) and its kappa was 0.655 (SE 0.11).

Contrast-enhanced ultrasound CEUS

In 36 (40.4%) patients, focal lesions were identified by CEUS, and 13 (14.6%) patients were suspected of having liver metastases (Fig. 1). In 23 (25.8%) patients, other focal lesions were noted but were not suspected of being metastases. In 53 (59.6%) patients, no focal lesions were observed by CEUS. These results are summarized in Table 2.

Of the 13 patients who were suspected of having liver metastases based on CEUS, 12 were confirmed.

One false-positive diagnosis of liver metastasis was made in an obese patient with fatty liver (steatosis) and a 23-mm, hypoechogenic lesion. Focal non-steatosis lesion was incorrectly diagnosed in the differential diagnosis as possible metastasis. Therefore, the PPV for the detection of liver metastases by CEUS was 92.3% (12/13). In total, 76 patients' liver metastases were not seen on CEUS, and 73 of these patients actually had no liver metastases, meaning that metastasis was undetected by CEUS in three patients who actually had metastasis. The same three malignant lesions were also undiagnosed by CT, and were only correctly diagnosed during surgery. Therefore, the NPV for the detection of liver metastases by CEUS was 96.1% (73/76).

Table 1. Focal lesions found by CT

Lesions	Frequency (n)	Percentage of n = 40
Malignant		
Metastases	9	22.5%
Metastases and cysts	1	2.5%
Metastases and hemangioma	3	7.5%
Metastases and steatosis	1	2.5%
Metastases, steatosis and hemangioma	1	2.5%
Metastases and abscess	1	2.5%
Total malignant	*16*	*40.0%*
Benign		
Cysts	13	32,5%
Cysts and hemangioma	4	10%
Cysts and steatosis	1	2.5%
Hemangioma, steatosis and calcifications	1	2.5%
Abnormalities too small or nonspecific to characterize	5	12.5%
Total non- malignant	*24*	*60.0%*
Total lesions	40	100%

The sensitivity of CEUS in the diagnosis of pancreatic tumor metastasis was 80% (12/15), its specificity was 98.6% (73/74) and its kappa was 0.833 (SE 0.08).

Computed tomography versus contrast-enhanced ultrasound

In total, 18/89 (20.2%) patients were suspected of having liver metastases on imaging. In suspected lesions, 11/18 (61.1%) patients were identified by both CT and CEUS, 2/18 (11.1%) patients only by CEUS and 5/18 (27.8%) patients only by CT.

Actual liver metastases were proven in 15 patients. In 11 (73.3%) patients, the suspected lesions were observed by both CT and CEUS. In one (6.7%) case, the metastasis was observed only by CEUS, whereas no patient metastases were diagnosed only by CT. Thus 12/15 (80%) patients had correctly suspected metastasis on an imaging (CEUS and/or CT) and 3/15 not suspected.

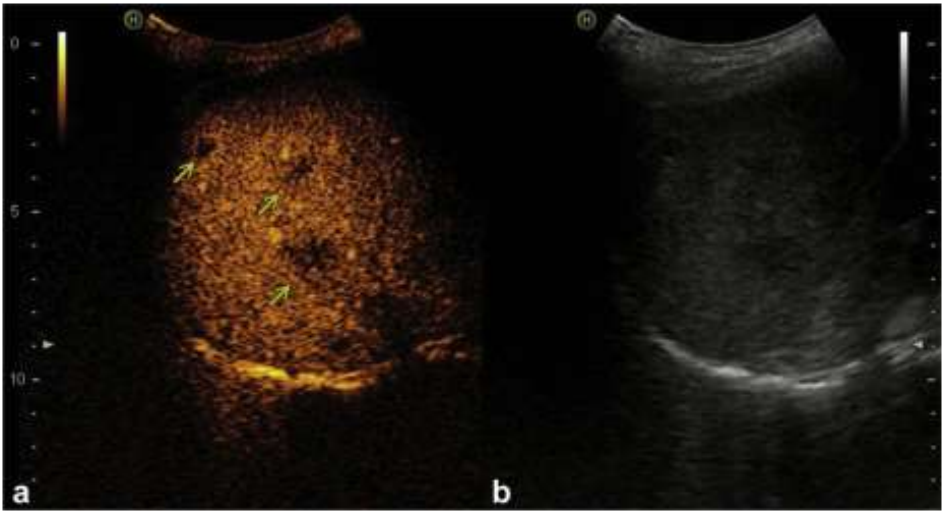

Fig. 1. Metastases detected by contrast-enhanced ultrasound. (a) Significant washout in multiple focal lesions 83 s after contrast IV injection. (b) Control native, non-enhanced ultrasound. Liver parenchyma heterogeneity can be easily misinterpreted.

From the 12 patients with metastasis, there were six patients with only one metastasis (diameter: 8, 12, 15, 18, 23 and 31 mm), one patient with two metastases (max 30 mm), one patient with three metastases (max 18 mm) and four patients with multiple metastases (8, 9, >10 and >10).

In three (20%) metastatic patients, no suspected lesions were found by either CT or CEUS. In these three patients with metastases diagnosed during operation, all were located on the liver surface, seen or palpated during open laparotomy. The average diameter cannot be correctly calculated (one was only 8 mm in diameter, and two had more than one metastasis with diameters not specified by the surgeon). Those three patients also had a longer mean interval between imaging and operation (CT 60 d, CEUS 31 d).

There was no significant difference between the sensitivities of the methods (73.3% vs. 80%, $p = 1.00$).

It would be interesting to investigate the performance for number and size of lesions; however, our study was too low-powered to test the answer, as the numbers were too small for a proper analysis (7/15 had only one metastasis [diameter 16.4 mm; 6 detected, 1 undetected by imaging], 2/15 had two or three metastases [max diameter 24 mm, all detected] and 6/15 had multiple [four detected, two undetected by imaging]). The sensitivity of different imaging methods relative to lesion number and size is as follows:

CEUS: one lesion, 85.7% (6/7); two to three lesions, 100% (2/2); and more than three lesions, 66.7% (4/6); <1 cm, 50.0% (1/2); 1–2 cm, 100% (6/6); and >2 cm, 71.4% (5/7).

CT: one lesion, 86.7% (6/7); two to three lesions, 100% (2/2); and more than three lesions, 50.0% (3/6); <1 cm, 50% (1/2); 1–2 cm, 83.3% (5/6); and >2 cm, 71.4% (5/7).

It could be suggested that larger and multiple lesions would be easier to detect as opposed to smaller individual ones. In our study, the one undetected lesion was only 8 mm and located on the liver surface, which made it even more difficult to visualize on any imaging technique. However, one third (2/6) of multiple metastases were missed. It is possible that other factors played a role, such as the previously mentioned interval (31 d between CEUS and operation); however, this interval did not differ from other studies in detection of liver metastasis from gastrointestinal cancer (4 wk in paper by Piscaglia [18]. The real importance of a shorter interval stays open and will be a topic for further clinical discussion.

Table 2. Focal liver lesions found by CEUS

Lesions	Frequency (n)	Percentage of n = 36
Malignant		
Metastases	7	19.4%
Metastases and cysts	2	5.5%
Metastases, cysts and hemangioma	1	2.8%
Metastases, hemangioma and steatosis	1	2.8%
Metastases and steatosis	2	5.5%
Total malignant	*13*	*36.1%*
Benign		
Cysts	16	44.4%
Hemangioma	1	2.8%
Cysts and steatosis	1	2.8%
Hemangioma and steatosis	1	2.8%
Abscess (bacterial)	1	2.8%
Abscess (amoeba)	1	2.8%
Focal non-steatosis	2	5.5%
Total non-malignant	*23*	*63.9%*
Total lesions	36	100%

CT and CEUS were both significant univariate predictors for the presence of liver metastasis in patients with pancreatic cancer. To compare CT and CEUS as predictors of liver metastasis, the results of both imaging methods were simultaneously entered into a logistic regression model. CEUS remained significant ($p < 0.001$), whereas CT did not add any additional information ($p = 0.292$).

A Venn diagram (Fig. 2) shows results of all possible metastases outcomes between both imaging methods (CT and CEUS) and the gold standard. Of notice is a large red area representing false-positive CT results.

Biliary drainage, stents and surgery

During CEUS, 6/89 (6.7%) patients had a percutaneous transhepatic cholangiography drain, 61/89 (68.5%) had a biliary stent and 4/89 (4.5%) had both a stent and a drain.

A total of 80 patients underwent surgery/diagnostic laparoscopy, whereas surgery was not performed in 17 patients. However, six (35.2%) of these patients did not undergo surgery because both CT and CEUS had already visualized suspicious lesions. In those patients, the lesions were proven to be malignant during further clinical observation.

Six patients who underwent surgery had actual liver metastases, diagnosed by perioperative biopsy. In three (50%) of those patients, the suspected lesions had already been observed by CEUS (CEUS alone in one patient; by both CEUS and CT in two patients). These lesions could not be histologically confirmed pre-operatively due to small size.

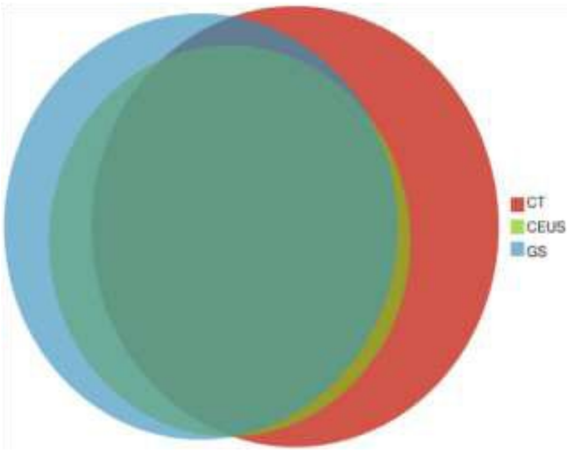

Fig. 2. Venn diagram showing results of all possible metastases outcomes between both imaging methods (CT and CEUS) and the gold standard. Of notice is a large red area representing false positive CT results. CT = computer tomography; CEUS = contrast-enhanced ultrasound; GS = gold standard.

DISCUSSION

The good performance of CEUS in detecting liver metastasis is already well known and established [19]. Still, in most studies, the patient population had liver metastases from various primary extra-hepatic tumors or only from colorectal cancer. Here, we present the first study in which CEUS was performed to assess the detection of liver metastases only in patients suspected of having pancreatic or periampullary carcinomas.

According to the results of this study, we can conclude that CEUS has a comparable sensitivity to CT in the detection of liver metastases (80% CEUS v. 73.3% CT, p = 1.00 by exact test) from suspected pancreatic or periampullary cancer. As already stated in a previous study [18], several metastatic lesions were detected by only one of the techniques, CT or CEUS, and this fact reflects complementarity of both methods with possible clinical implementation of both modalities in clinical practice. Sensitivity of CEUS and CT in detecting metastases was somehow lower in our study compared to previous reports (CEUS: 80% – 95%, CT 76% – 91% [20]); whether this reflects different characteristics of pancreatic adenocarcinoma remains an open question.

However, the main difference between CT and CEUS in our study was the ability of CEUS to differentiate between metastasis and accidental liver lesions that were later shown to be benign (cysts in two patients and lesions that were difficult to correctly characterize on CT in three patients, one due to suboptimal scan quality, one hypervascular lesion that turned out to be shunt [on MRI] and one lesion thought to be a metastasis or a focal bile duct dilation that turned out to be the latter on CEUS). In all these cases, CT yielded a higher number of false-positive results and thus a lower PPV (68.7% vs. 92.3%).

In a logistic regression model, CEUS remained significant ($p < 0.001$), whereas CT did not provide any additional information.

CEUS is accurate in distinguishing between malignant and benign liver lesions. We should keep in mind that benign liver lesions can be found at the same frequency in patients with liver metastases as in the healthy population. In our study, 29% of the patients had benign focal lesions in their livers that were unrelated to pancreatic cancer. CEUS may thus reduce the number of unnecessary imaging procedures and invasive examinations and even prevent unnecessary laparotomies. Thus far, only a few false-positive malignant liver findings have been observed by CEUS, mainly due to abscesses, necrosis, focal scar tissue, sarcoidosis or inflammatory pseudotumors [21].

Several studies have evaluated the costs of liver CEUS compared with CT. The main conclusion of those studies was that CEUS is a cost-efficient method for the detection of focal liver lesions during first-line diagnosis compared with first-line contrast CT or first-line contrast MRI [22-23]. CT cannot be replaced by CEUS and is still necessary to define the local resectability of the primary tumor, thus the comparison of cost efficiency between first-performed diagnostic CT and CEUS does not arise. Still, the costs of unnecessary laparotomies and further imaging can be prevented when CEUS is adopted as an indispensable part of the diagnostic algorithm, perhaps in combination with percutaneous biopsy to characterize unclear lesions.

Even for multi-detector CT, the ability to detect small hepatic metastases is approximately 75% [24-25]. CT has difficulty in differentiating small hypo-vascular liver metastasis from small benign lesions that also appear hypovascular, such as cysts and hemangiomas. The sensitivity of CEUS in detecting liver metastasis is generally approximately 86%–94% [26]. During CEUS, the metastasis typically appears as a very short arterial enhancement (peripheral or diffuse) or remains isoechogenic, followed by rapid washout in the portal phase. The primary advantages of CEUS are its realtime scanning capability and high temporal resolution. A CT obtained at a single time-point can miss shorter, early enhancements. Additionally, in contrast to CT, rapid and complete washout in the portal phase is an invariable characteristic of metastasis during CEUS [27].

In primary pancreas tumor staging, CT is mandatory and cannot be replaced by CEUS. However, complementary CEUS after CT scan can rule out both false-positive (i.e., small or unclear lesions) and false-negative CT findings in the liver, and so CEUS can hold an important role in the patient's workup.

The limitations of this study include small sample size. Whether a longer interval between imaging and operation can play a role in false-negative CT and CEUS is an open question, as our performance results come from current clinical practice. It would be also nice to include size and number of lesion study performance; however, our study power was too low.

Several limitations of ultrasound also remain, such as its operator dependence and the limited visibility of certain portions of the liver, especially in an obese patient with liver steatosis. In our series, the one false-positive diagnosis of metastasis was due to liver steatosis in which an area of focal non-steatosis mimicked a hypoechogenic tumor. This lesion was observed but was incorrectly interpreted. In a case of doubt we can increase CEUS performance by repeating contrast agent injection(s) and/or with ultrasound setting adjustment.

CONCLUSION

CEUS can improve the detection of liver metastases in patients with suspected pancreatic cancer in comparison with CT. Our data suggest that CEUS can improve the determination of benign versus malignant liver lesions, detect false-positive or indeterminate CT results and spare the patient unnecessary diagnostic procedures. Therefore, CEUS could be recommended as a part of screening protocol before pancreatic resection.

Acknowledgment— The study was partially funded by ZonMW, The Netherlands, dossier number 170991010. Period 2009–2011.

BIBLIOGRAPHY

[1] American Cancer Society, "Cancer Facts & Figures," Atlanta, 2013.

[2] H. Reidiger, T. Keck, U. Wellner, A. zur Hausen, U. Adam, U. Hopt and F. Makowiec, "The Lymph Node Ratio Is the Strongest Prognostic Factor After Resection of Pancreatic Cancer," *J Gastrointest Surg,* pp. 1337-44, 13(7) Jul 2009.

[3] H. Braat, M. Bruno, E. Kuipers and M. Peppelenbosch, "Pancreatic Cancer: Promise for Personalised Medicine?," *Cancer Lett,* pp. 1-8, 318(1) May 1 2012.

[4] S. Sener, A. Fremgen, H. Menck and D. Winchester, "Pancreatic Cancer: A Report of Treatment and Survival Trends for 100,313 Patients Diagnosed From 1985-1995, Using the National Cancer Database," *J Am Coll Surg,* pp. 1-7, 189(1) Jul 1999.

[5] D. Sahani, Z. Shah, O. Catalano, G. Boland and W. Brugge, "Radiology of Pancreatic Adenocarcinoma: Current Status of Imaging," *J Gastroenterol Hepatol,* pp. 23-33, 23(1) Jan 2008.

[6] N. Balci and R. Semelka, "Radiologic Diagnosis and Staging of Pancreatic Ductal Adenocarcinoma," *Eur J Radiol,* pp. 105-12, 38(2) May 2001.

[7] K. Holzapfel, C. Reiser-Erkan, A. Fingerle, M. Erkan, M. Eiber, E. Rummeny, J. Kleef and J. Gaa, "Comparison of Diffusion-Weighted MR Imaging and Multidetector-Row CT in the Detection of Liver Metastases in Patients Operated for Pancreatic Cancer," *Abdom Imaging,* pp. 179-84, 36(2) Apr 2011.

[8] U. Motosugi, T. Ichikawa, H. Morisaka, H. Sou, A. Muhi, K. Kimura, K. Sano and T. Araki, "Detection of Pancreatic Carcinoma and Liver Metastases With Gadoxetic Acid-Enhanced MR Imaging: Comparison With Contrast-Enhanced Multi-Detector Row CT," *Radiology,* pp. 446-53, 260(2) Aug 2011.

[9] M. Nielsen and A. Bang, "Contrast Enhanced Ultrasound in Liver Imaging," *Eur J Radiol,* pp. S3-8, 51 Suppl Jun 2004.

[10] M. Brannigan, P. Burns and S. Wilson, "Blood Flow Patterns in Focal Liver Lesions at Microbubble-Enhanced US," *Radiographics,* pp. 921-35, 24(4) Jul-Aug 2004.

[11] E. Quaia, F. Calliada, M. Bertolotto, S. Rossi, L. Garioni, L. Rosa and R. Pozzi-Mucelli, "Characterization of Focal Liver Lesions With Contrast-Specific US Modes and a Sulfur Hexafluoride-Filled Microbubble Contrast Agent: Diagnostic Performance and Confidence," *Radiology,* pp. 420-30, 232(2) Aug 2004.

[12] I. Sporea, R. Badea, A. Martie, R. Sirli, M. Socaciu, A. Popescu and M. Danila, "Contrast Enhanced Ultrasound for the Characterization of Focal Liver Lesions," *Med Ultrason,* pp. 38-44, 13(1) Mar 2011.

[13] Y. Dai, M. Chen, S. Yin, K. Yan, Z. Fan, W. Wu, Y. Wang and W. Yang, "Focal Liver Lesions: Can SonoVue-enhanced Ultrasound Be Used to Differentiate Malignant From Benign Lesions?," *Invest Radiol,* pp. 596-603, 42(8) Aug 2007.

[14] H. Jang, H. Yu and T. Kim, "Contrast-enhanced Ultrasound in the Detection and Characterization of Liver Tumors," *Cancer Imaging,* pp. 96-103, 9(1) Nov 6 2009.

[15] C. Dietrich, W. Kratzer, D. Strobe, E. Danse, R. Fessl, A. Bunk, U. Vossas, K. Hauenstein, W. Koch, W. Blank, M. Oudkerk, D. Hahn and C. Greis, "Assessment of Metastatic Liver Disease in Patients With Primary Extrahepatic Tumors by Contrast-Enhanced Sonography Versus CT and MRI," *World J Gastroenterol,* pp. 1699-705, 12(11) Mar 21 2006.

[16] T. Albrecht, M. Blomley, L. Bolondi, M. Claudon, J.-M. Correas, D. Cosgrove, L. Greiner, K. Jager, N. De Jong, E. Leen, R. Lencioni, D. Lindsell, A. Martegani, L. Solbiati, L. Thorelius,

F. Tranquart, H. Weskott, T. Whittingham and EFSUMB Study Group, "Guidelines for the Use of Contrast Agents in Ultrasound. January 2004," *Ultraschall Med,* pp. 249-56, 25(4) Aug 2004.

[17] E. Deerenberg, J.-W. Poley, J. Hermans, S. Ganesh, E. van der Harst and C. van Eijck, "Role of Endoscopic Ultrasonography in Patients Suspected of Pancreatic Cancer With Negative Helical MDCT Scan," *Dig Surg,* pp. 398-403, 2011.

[18] F. Piscaglia, F. Corradi, M. Mancini, F. Giangregorio, S. Tamberi, G. Ugolini, B. Cola, A. Bazzocchi, R. Righini, P. Pini, F. Fornari and L. Bolondi, "Real Time Contrast Enhanced Ultrasonography in Detection of Liver Metastases From Gastrointestinal Cancer," *BMC Cancer,* p. 171, 7 Sep 3 2007.

[19] D. Strobel, K. Seitz, W. Blank, A. Schuler, C. Dietrich, A. von Herbay, M. Friedrich-Rust and T. Bernatik, "Tumor-specific Vascularization Pattern of Liver Metastasis, Hepatocellular Carcinoma, Hemangioma and Focal Nodular Hyperplasia in the Differential Diagnosis of 1,349 Liver Lesions in Contrast-Enhanced Ultrasound (CEUS)," *Ultraschall Med,* pp. 376-82, 30(4) Aug 2009.

[20] L. Larsen, "Role of Contrast Enhanced Ultrasonography in the Assessment of Hepatic Metastases: A Review," *World J Hepatol,* pp. 8-15, 2(1) Jan 27 2010.

[21] C. Dietrich, A. Ignee, J. Trojan, C. Fellbaum and G. Schuessler, "Improved Characterisation of Histologically Proven Liver Tumours by Contrast Enhanced Ultrasonography During the Portal Venous and Specific Late Phase of SHU 508A," *Gut,* pp. 401-05, 53(3) Mar 2004.

[22] F. Giesel, S. Delorme, R. Sibbel, H.-U. Kauczor and M. Krix, "[Contrast-enhanced Ultrasound for the Characterization of Incidental Liver Lesions - An Economical Evaluation in Comparison With Multi-Phase Computed Tomography]," *Ultraschall Med,* pp. 259-68, 30(3) Jun 2009.

[23] R. Sirli, I. Sporea, A. Martie, A. Popescu and M. Danila, "Contrast Enhanced Ultrasound in Focal Liver Lesions--A Cost Efficiency Study," *Med Ultrason,* pp. 280-5, 12(4) Dec 2010.

[24] E. Manak, S. Merkel, P. Klein, T. Papadopoulos, W. Bautz and U. Baum, "Resectability of Pancreatic Adenocarcinoma: Assessment Using Multidetector-Row Computed Tomography With Multiplanar Reformations," *Abdom Imaging,* pp. 75-80, 34(1) Jan-Feb 2009.

[25] S. Satoi, H. Yamamoto, S. Takai, N. Tanigawa, A. Komemushi, H. Yanagimoto, H. Toyokawa, Y. Matsui, H. Mergental and Y. Kamiyama, "Clinical Impact of Multidetector Row Computed Tomography on Patients With Pancreatic Cancer," *Pancreas,* pp. 175-79, 34(2) Mar 2007.

[26] J. Hohmann, T. Albrecht, A. Oldenburg, J. Skrok and K.-J. Wolf, "Liver Metastases in Cancer: Detection With Contrast-Enhanced Ultrasonography," *Abdom Imaging,* pp. 669-81, 29(6) Nov-Dec 2004.

[27] S. Wilson, T. Kim, H.-J. Jang and P. Burns, "Enhancement Patterns of Focal Liver Masses: Discordance Between Contrast-Enhanced Sonography and Contrast-Enhanced CT and MRI," *AJR Am J Roentgenol,* pp. W7-W12, 189(1) Jul 2007.