—Original Article—

Discriminating chronic pancreatitis from pancreatic cancer: Contrast-enhanced EUS and multidetector computed tomography in direct comparison

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ABSTRACT

Background and Objectives: To compare the ability of multidetector computed tomography (MDCT) and contrast-enhanced EUS to discriminate chronic pancreatitis (CP) from pancreatic ductal adenocarcinoma (PDAC). **Subjects and Methods:** A total of 215 patients (age: 62 ± 15 years, sex: f/m 80/135) were included in this retrospective study. All patients were examined by conventional endoscopic B-mode and contrast-enhanced high mechanical index EUS (CEHMI-EUS). CELMI-EUS was performed in 159 patients and endoscopic sonoelastography (ESE) in 210 patients. MDCT was carried out in 131 patients as part of their clinical work-up. Radiological reports were retrospectively analyzed. Final diagnosis was achieved by biopsy and evaluation of cytological specimens collected was performed by EUS-FNA, surgery, or follow-up of 12 months or more in patients with benign findings. In a subgroup of 100 patients, all diagnostic five methods were performed, and head-to-head analysis was performed. **Results:** Sensitivity and specificity for MDCT were 89% and 70% and for CEHMI-EUS were 96% and 91%, respectively. Sensitivities and specificities for EUS were 92% and 63% for B-Mode EUS, 96% and 38% for ESE, and 82% and 76% for CELMI-EUS, respectively. In the head-to-head analysis, each modality had shown lower numbers for specificity than shown in the overall group analysis because of high drop-out rate. EUS-FNA for PDAC had a sensitivity of 96% and a specificity of 100%. **Conclusions:** Contrast-enhanced EUS is a reliable tool in discriminating PDAC from CP.

Key words: Adenocarcinoma, elastography, guidelines, pancreas, pancreatitis

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive neoplasm and accounts for 331,000 deaths annually worldwide. It is the seventh leading cause of cancer-related death worldwide, despite a relatively low but increasing incidence.[1] Surgical resection

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represents the only potentially curative treatment[2,3] but is often not available because only about 20% of PDACs are detected at an operable stage.[4] This might explain why this tumor shows a 5-year overall survival as low as 5%–7%,[2,5-8] with almost no improvement over the past three decades,[8] except for very small PDAC and functional neuroendocrine tumors.[9,10] Although technology improves, it still remains a challenge to discriminate between PDAC and chronic pancreatitis (CP).[11,12] CP can present itself mass-forming,[13,14] and at the same time, it is a major risk factor for PDAC.[15,16] Other differential diagnoses have to be taken into account, for example, autoimmune pancreatitis.[17-21] The differentiation between these two diseases is essential to consecutive treatment and prognosis. Moreover, too often, surgical resection reveals misdiagnosis of a benign lesion.[22,23] Therefore, it is crucial to find less invasive diagnostic methods to protect patients from unnecessary risks of operation.

Multidetector computed tomography (MDCT) is an important tool in every day clinical practice that has greatly improved our capability of depicting pancreatic masses.[24] It is recommended as a standard diagnostic procedure for staging when PDAC is suspected.[2,4,25,26] However, it has its limitations: MDCT is not always very useful in showing slight changes in soft tissue,[27] and discrimination of focal pancreatitis and pancreatic cancer is a well-known dilemma.[11,28,29] Furthermore, it exposes the patient to relatively high doses of radiation.[30]

Several EUS submodalities have been developed over the past 35 years[31,32] that allow real-time imaging:[33] The conventional B-mode EUS imaging was complemented by the use of ultrasound contrast agents (UCAs).[34] UCAs are coated microbubbles that cannot leave the blood vessels by diffusion. Modern UCAs pass pulmonary circulation and have prolonged survival, thereby allowing evaluation of vascular structures over a longer period.[34-36] Contrast-enhanced high mechanical index (CEHMI) EUS is helpful in detecting and characterizing macrovessels inside an area of interest.[37] Contrast-enhanced low mechanical index (CELMI) EUS, on the other hand, is a tool for comparing capillary vascularization patterns in a lesion with that of adjacent tissue.[38] Endoscopic sonoelastography (ESE) is a method that tests the hardness of tissue by compressing it and then evaluating the change in images taken before and afterward.[33] It presumes less elasticity – meaning greater hardness – in cancer than in normal or inflamed tissue.

The main purpose of this study was to compare diagnostic value of MDCT and CEHMI-EUS in differentiating between PDAC and CP. The data collected allowed comparison of these results with those of B-mode EUS, CELMI-EUS, and ESE as a secondary goal.

SUBJECTS AND METHODS

Patients

Over a period of 5 years (November 2008–December 2013), 225 patients with suspected pancreatic mass underwent diagnostic procedures at the Department of Internal Medicine II, Hospital Meiningen. A total of 124 patients were finally diagnosed with PDAC. The gold standard was either cytology (Papanicolaou [PAP] IV–V) or surgery with subsequent histopathological examination. The remaining 91 patients were diagnosed with CP. If the patients still showed no clinical or endosonographic signs of malignancy after 1 year, we regarded this as proof for the correct benign diagnosis because the mean survival of untreated pancreatic carcinoma is reported to be only about 6 months from the time of diagnosis.

Finally, a total of 215 patients (age: 62 ± 15 years, sex: f/m 80/135) were included in the study.

All patients gave their informed consent to participate in this study.

Exclusion criteria

We excluded patients with neuroendocrine tumor of the pancreas (n = 2) as well as gastric adenocarcinoma (n = 1), ampullary cancer (n = 1), distal cholangiocarcinoma (n = 1), bronchial carcinoma metastasis (n = 1), and renal cell carcinoma metastasis (n = 1). Furthermore, we excluded patients with CP in which no follow-up information could be obtained (n = 3).

Methods

In 131 patients, contrast-enhanced MDCT (Somatom Force, Siemens, Germany) had been performed as part of their clinical work-up. 110 ml Ultravist® (Bayer, Germany) served as a contrast agent. The scans were analyzed by four radiologists at the

time of diagnosis. For the purpose of this study, we retrospectively analyzed the radiological reports and used the following criteria: MDCT-criteria for CP were calcifications, formation of pseudocysts, dilatation of the main pancreatic duct and/or main biliary duct, parenchymal atrophy, focal or whole-organ enlargement, changes in peripancreatic fat tissue, or Gerota fascia.[28,39] In the case of signs suspicious for malignancy (pancreatic mass – usually with a hypodense center and peripheral contrast enhancement – or invasion of surrounding organs or tissue), PDAC was assumed. PDAC was assumed as hypodense, hypovascular – hence hypoenhancing – mass.[40] If there were no clear signs of malignancy, we assumed CP. However, neither the radiologists creating the reports at the time of diagnosis nor the author who analyzed the radiological reports retrospectively was blinded to the results of the other diagnostic procedures or the patient history.

EUS was performed for targeting and measurement of pancreatic lesions in all patients using Pentax EUS Probe URK 38 (Pentax Co, Ltd., Japan) and UT series and a Hitachi Preirus (Hitachi, Ltd., Japan) ultrasound machine. The patients were sedated with propofol and monitored according to the guidelines. First, the lesion was diagnosed using conventional B-mode, followed using the previously described criteria.[37]

In 210 patients, ESE was performed to investigate the lesion. For 2 min, the stiffness of the targeted tissue was compared to the surrounding normal tissue. Blue coding was interpreted as harder than the surrounding pancreatic tissue, and therefore, tumorous tissue, while red and green coding was taken as a sign for focal CP.

In 159 patients, low mechanical index ultrasonography was performed. The ultrasound machine is required to be equipped with adapted wideband pulsed inversion software so that it can use contrast harmonic imaging. It allows detecting second harmonic waves that emit from the microbubbles at a low mechanical index but not from contiguous tissue. Because the microbubbles do not burst at low acoustic pressures, CELMI-EUS permits real-time imaging of the contrast agent washing in and out of the observed area. With the machine in low mechanical index mode, we injected 4.8 ml of SonoVue (Bracco, Italy) into a peripheral vein, followed by 10 ml of saline. Over a time period of 2 min after influx of the contrast agent, enhancement of the lesion was compared to its surroundings. Hypoenhancement was regarded as a sign of neoplasia, whereas iso-or hyper-enhancement was classified as CP.

High mechanical index EUS was carried out by applying another 4.8 ml of SonoVue that was administered along with 10 ml of saline. After administering the contrast agent, blood vessels within the lesion were detected using color Doppler with adjusted repetition frequency and wall filters. Gain was set as low as possible to avoid noise artifacts. Classification of the lesion was done using pulsed-wave (PW) Doppler. Continuous flow pattern was used as an indicator for venules, whereas pulsatile flow pattern was indicating arterioles. The mean time of evaluation was 3 min. After this, the contrast agent has diluted too much for adequate enhancement. If only arterioles were detectable in a mass, we assumed PDAC. If both arterioles and venules were present, the mass was qualified as CP.

Suspected lesions were biopsied using a 22-G aspiration biopsy needle (Cook, Ireland) in 130 patients. The material was dried, stained, and later analyzed by a cytopathologist.

Based on the results of all examinations and clinical appearance, 47 patients were admitted to surgery. The pathological results were acknowledged as the gold standard. Otherwise, we used the cytopathological results for final diagnosis. In patients with suspected CP, follow-up of at least 12 months was also accepted as gold standard in benign lesions.

If necessary, other reference imaging (*i.e.*, magnetic resonance imaging) was performed as part of their clinical work-up, but the results were not included in data analysis.

Statistical analysis

Sensitivity was defined as correctly classified PDAC cases divided by the number of total PDAC cases (true positives/true positives + false negatives). Specificity was defined as the number of correctly classified CP cases divided by the number of total CP cases (true negatives/true negatives + false positives).

RESULTS

Contrast-enhanced MDCT detected PDAC in 81 out of 91 patients (sensitivity = 89%) but could only correctly classify CP in 28 of 40 patients (specificity = 70%). Good-quality imaging was achieved using conventional B-mode EUS in all cases. It presented almost the same

sensitivity (92%, 114 of 124 PDAC) but was worse than MDCT in terms of specificity (63%, 57 of 91 CP). ESE showed outstanding cancer detection (116 of 121 PDAC, sensitivity = 96%) but was unreliable in differentiating it from CP (34 of 89 CP, specificity = 38%). CELMI-EUS was performed on patients undergoing EUS examination only after January 2010 (installation of the necessary software). CELMI-EUS failed to detect cancer at a high rate (72 of 88 PDAC, 82%). Moreover, CP was correctly classified in only 54 of 71 cases (specificity = 76%).

CEHMI-EUS has shown earlier to be a reliable technique for the differential diagnosis of pancreatic diseases.[41,42] CEHMI-EUS proved to be the best method in discriminating between PDAC and CP: CEHMI-EUS achieved correct diagnosis in 119 out of 124 patients with pancreatic carcinomas (sensitivity = 96%) and 83 out of 91 patients with CP (specificity = 91%).

In a subgroup of 100 patients, all five methods have been performed. In those patients, a head-to-head analysis of the four EUS methods compared with the state-of-the-art CT scan achieved following results. CEHMI-EUS was still the best method with sensitivity at 94% and specificity at 76%. The comparatively low specificity here is due to a high drop-out rate for this group. A high number of patients had not received MDCT examinations because it was not deemed necessary at the time of diagnosis. In comparison, sensitivity and specificity for MDCT were 90% and 64%, respectively. Sensitivity and specificity for B-mode EUS, ESE, and CELMI-EUS were 90% and 36%, 96% and 27%, and 81% and 70%, respectively.

EUS-guided fine needle aspiration (EUS-FNA) was performed in 130 patients. Correct diagnosis of PDAC was achieved in 94 out of 98 cases (sensitivity = 96%) and in 32 out of 32 patients with CP (specificity = 100%).

Gold standard

If there were clearly tumor cells in the tissue (PAP IV and V), we regarded this as proof for carcinoma (n = 90). If there were clearly no tumor cells (PAP I–III), we assumed CP but final diagnosis was achieved by follow-up after 1 year or more (n = 76). In two patients, follow-up was <12 months (9 and 11 months) but the results of contrast-enhanced EUS and EUS-FNA were negative for carcinoma. In 47 patients, diagnosis was confirmed through surgery (34 cases of carcinoma, 13 cases of CP).

Results are summarized in Table 1. The results of the subgroup analysis are shown in Table 2.

DISCUSSION

It could be shown that CEHMI-EUS can detect PDAC and differentiate it from CP more effectively than MDCT. It also has a higher sensitivity and specificity for PDAC than conventional B-mode EUS, ESE, and CELMI-EUS. CEHMI-EUS should be considered a standard procedure in patients with CP and suspected PDAC.

Table 1. Comparison of methods, results

	n	MDCT (%)	B-mode EUS (%)	ESE (%)	CELMI-EUS (%)	CEHMI-EUS (%)	EUS-FNA (%)
Pancreatic cancer (sensitivity)	124	81/91 (89)	114/124 (92)	116/121 (96)	72/88 (82)	119/124 (96)	94/98 (96)
CP (specificity)	91	28/40 (70)	57/91 (63)	34/89 (38)	54/71 (76)	83/91 (91)	32/32 (100)
Accuracy ([TP + TN]/all patients)		83	80	71	79	94	97
PPV (TP/[TP + FP])		87	77	68	81	94	100
NPV (TN/[TN + FN])		74	85	87	77	94	89

PDAC: Pancreatic ductal adenocarcinoma, CP: Chronic pancreatitis, CEHMI-EUS: Contrast-enhanced high mechanical index EUS, CELMI-EUS: Contrast-enhanced low mechanical index EUS, FNA: Fine needle aspiration, ESE: Endoscopic sonoelastography, MDCT: Multidetector computed tomography, PPV: Positive predictive values, NPV: Negative predictive values, TP: True positive, TN: True negative, FP: False positive, FN: False negative

Table 2. Subgroup analysis

	n	MDCT (%)	B-Mode EUS (%)	ESE (%)	CELMI-EUS (%)	CEHMI-EUS (%)
Pancreatic cancer (sensitivity)	67	60/67 (90)	60/67 (90)	64/67 (96)	54/67 (81)	63/67 (94)
CP (specificity)	33	21/33 (64)	12/33 (36)	9/33 (27)	23/33 (70)	25/33 (76)
Accuracy ([TP + TN]/all patients)		81	72	73	77	88
PPV (TP/[TP + FP])		83	74	73	84	89
NPV (TN/[TN + FN])		75	63	75	64	86

CP: Chronic pancreatitis, CEHMI-EUS: Contrast-enhanced high mechanical index EUS, CELMI-EUS: Contrast-enhanced low mechanical index EUS, FNA: Fine needle aspiration, ESE: Endoscopic sonoelastography, PPV: Positive predictive values, NPV: Negative predictive values, TP: True positive, TN: True negative, FP: False positive, FN: False negative

In our study, CT showed overall good tumor detection (sensitivity of 89%) but unsatisfactory differentiation between CP and PDAC (specificity of 70%). We found comparable results in the head-to-head test (90% and 64%). Sensitivity of MDCT for PDAC is reported to be as high as 86%–97%[24,43-52] although some studies report it to be much lower.[53,54] Few authors have reported specificity of MDCT using CP as control group rather than patients without pancreatic pathology. Schima *et al.*[55] report that out of ten cases of focal CP in their study, only four were diagnosed correctly. Six were deemed to be carcinomas after CT image interpretation. Lu *et al.*[56] showed that perfusion CT imaging can be helpful in this regard. Other authors have emphasized the utility of perfusion CT imaging in pancreatic diseases,[57,58] but it is not yet widely used. Yamada *et al.*[44] found specificity to be at 83% using enhancement patterns to differentiate between the two conditions.

There are some other limitations also found in our study. Prokesch *et al.*[59] found that up to 11% of PDAC is isoattenuating on MDCT. It is worth mentioning that their study included only a small number of patients (n = 53) and that their selection was biased. Still, these numbers were confirmed by Yoon *et al.*[29] in a study with a higher number of patients (n = 163). They found that 27% of tumors 20 mm or smaller in diameter and 13% of tumors 21–30 mm in size were isoattenuating. Both groups showed that secondary signs are very helpful in cases of isoattenuation. These include pancreatic duct interruption, dilatation of pancreatic or common bile duct, as well as mass effect and convex contour abnormalities. However, the same secondary signs can occur in mass-forming CP.[14,60] This regularly makes differential diagnosis difficult using MDCT scans. Neff *et al.*[61] showed early that inflammatory masses occur regularly in patients with CP. In their study, 19 out 210 patients with CP presented mass formation that later proved to be benign.

In addition, CP and PDAC can both produce a high degree of fibrosis in pancreatic tissue, making it even harder to distinguish one from the other. Kim *et al.*[14] found that pancreatic masses can be difficult to diagnose in either of two cases: (1) fibrosis is present in the whole organ so that a mass will not be demarcated and (2) fibrosis in a chronically inflamed pancreas can be focal without enlargement of the whole organ, therefore demarcating a mass that is not malignant. Scialpi *et al.*[62] have recently shown another pitfall of pancreatic MDCT imaging: They found that (a) a high degree of fibrosis in nontumorous tissue and (b) a low degree of fibrosis in the tumor cause the lesion to be isodense on MDCT imaging. They also found that the localization of the lesion in corpus or tail has negative impact on the imaging results.

B-mode EUS was highly sensitive (90%) in tumor detection but did not prove to be a reliable tool for discriminating between PDCA and CP. This confirms the results of previous studies[23,37,41,42,63,64] although some authors report better specificity.[65-67]

Endoscopic sonoelastography

ESE has recently been discussed controversially because the results were inconsistent.[42,68-72] In our study, we found that ESE not only identifies almost all of the tumors but also falsely declares benign masses to be malignant. In a multicenter study,[73] sensitivity and specificity of ESE were reported to be 93% and 66%, respectively. These numbers are based on a mean hue histogram value cutoff of 175. According to their calculations, sensitivity and specificity were found to be 79% and 79%, respectively, after adjusting the cutoff value to 185. The use of an artificial neural network could improve specificity of ESE. Săftoiu *et al.*[74] reported sensitivity and specificity to be at 91% and 88%, respectively. In a later study,[75] they found these numbers to be 88% and 83%, respectively.

Contrast-enhanced EUS

CELMI-EUS is a relatively new modality that has first been described in 2005[76] and was not commercially available until 2009.[77] The technique, prerequisites, and applications have been recently described.[78-81]

CELMI-EUS depicts parenchymal perfusion and also provides information on microvasculature.[33,38] In CELMI-EUS, PDAC usually presents itself hypoenhancing compared to adjacent tissue while mass-forming CP is expected to be isoenhancing or sometimes hyperenhancing[35,42,82,83] but can even be nonenhancing.[84] Napoleon *et al.*[85] concluded that CELMI-EUS is an adequate tool for the task of distinguishing carcinoma from inflammatory mass. Gheonea *et al.*[83] proposed a quantitative analysis using time–intensity curves to discriminate these diseases. In contrast, Seicean *et al.* found a significant percentage of hypoenhancing masses in patients with CP, and the authors suspect that this could be due to a high degree of fibrosis occurring in patients with severe

CP.[86] They also propose a quantitative – using an uptake ratio index – rather than a qualitative approach. Fusaroli *et al.*[87] also pointed out that CP masses can be hypoenhancing in CELMI-EUS. In their study, only four out of 13 patients with CP were correctly diagnosed. The relatively low numbers for sensitivity and specificity in our study reflect those of a previous publication.[42] One explanation for this might be a high percentage of carcinomas with well-developed capillaries in our study.

EUS-FNA is a reliable tool for the evaluation of pancreatic masses.[88] In our study, four out of 98 patients with PDAC were misdiagnosed by EUS-FNA. This is likely due to a sampling error. In these cases, the aspiration needle collected tissue that was not containing cancer cells. Sensitivity was very good (96%) although the presence of CP is known as a pitfall, decreasing the sensitivity of this procedure.[89] Consequently, it is desirable to find a diagnostic tool that is less invasive and possibly even more accurate.[90] There were no false positive results in EUS-FNA, leaving specificity at 100%. It is worth pointing out that not all lesions were punctured if there was a very high probability for carcinoma or a benign process. This may have caused a selection bias.

CEHMI-EUS uses Doppler analysis for the evaluation of macrovessels inside an area of interest.[35,91] While continuous duplex (PW Doppler + color mode) scanning allows detecting the presence of arterioles and venules in a region of interest, the contrast-enhanced color Doppler mode is useful in characterizing the architecture of those vessels.[35,37]

Dietrich *et al.*[92] point out the value of contrast-enhanced Doppler analysis: they report a sensitivity of 92% and specificity of 100% in a group of 62 patients, using color Doppler analysis and hypovascularity as their main criterion for carcinoma. However, they excluded patients with CP.

However, several studies report on the utility of contrast-enhanced Doppler analysis for distinguishing PDAC from CP:

Using contrast-enhanced EUS power Doppler imaging in a group of 23 patients, Becker *et al.*[93] report sensitivity and specificity to be 94% and 100%, respectively.

Săftoiu *et al.*[94] used power Doppler analysis without contrast enhancement in a series of 42 patients and they report sensitivity and specificity to be 93% and 77%, respectively. They were able to increase these numbers by evaluating the presence or absence of collaterals to 97% and 92%, respectively.

In another study, Săftoiu *et al.*[95] combined contrast-enhanced power Doppler and real-time sonoelastography to differentiate pancreatic masses. Applying "hypovascular" and "hard" as main criteria for carcinoma, they found sensitivity to be at 76% and specificity to be at 95%.

Hocke *et al.*[96] found that analyzing the resistance index of arterial vessels inside a mass can helpful in discriminating pancreatic masses.

Other studies including more patients confirmed CEHMI-EUS to be an important tool in the differential diagnosis of pancreatic cancer *versus* CP that offers high diagnostic accuracy.[37,41,42]

Several authors have pointed out the susceptibility of CEHMI-EUS to artifacts such as "blooming."[31,83,85,97] To avoid the occurrence of such artifacts, we adjusted pulse repetition frequency and wall filters as described previously[37,41] and also adjusted gain as low as possible to obtain optimal imaging quality. Using these settings, we were able to achieve satisfactory imaging in all patients.

Modern EUS techniques have become available in recent years. The use of three-dimensional contrast-enhanced EUS techniques might improve our ability to depict pancreatic masses even further.[98] However, currently, CEHMI-EUS still seems to be the most effective tool in discriminating PDAC from CP.

In particular, CEHMI-EUS compares favorably to MDCT because it is more reliable in differentiating PDAC from CP. In the head-to-head analysis, both methods showed a similar sensitivity (94% for CEHMI and 90% for MDCT). However, specificity of CEHMI-EUS was lower than expected (76%) but still better than MDCT (64%). Thus, more research needs to be conducted to confirm superiority of CEHMI-EUS over MDCT in this regard.

The limitations of our study can be summarized as follows:

- This a single-center study

- All EUS procedures were carried out by one examiner (MH)
- The examiners of CT imaging and the EUS examiner were not blinded to the patients' record or the results of other diagnostics at the time of diagnosis. Furthermore, the author analyzing MDCT reports retrospectively was not blinded to the patients' history. This may have led to bias and altered the results of this study.

CONCLUSIONS

MDCT is mandatory for staging of PDAC. Yet, it is not specific enough for reliable differentiation in patients with underlying CP. B-mode EUS is an adequate tool for detecting and measuring pancreatic masses but fails in the presence of CP. ESE is highly sensitive for PDAC but has a very low specificity and therefore cannot be generally recommended for clinical practice in patients with CP and suspected PDAC. CELMI-EUS could not confirm the good results of previous studies without CP. CEHMI-EUS can detect PDAC and differentiate it from CP more effectively than MDCT. It also has a higher sensitivity and specificity for PDAC than conventional B-mode EUS, ESE, and CELMI-EUS.

Thus, CEHMI-EUS should be considered a standard procedure when pancreatic carcinoma is suspected in a patient and as a follow-up tool in patients with CP.

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Conflicts of interest
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