Can We Rely On Contrast-enhanced CT to Identify Pancreatic Ductal Adenocarcinoma? A Population-Based Study in Sensitivity and Factors Associated with False Negatives

ABSTRACT

Objectives: To determine the sensitivity of contrast-enhanced computed tomography (CECT) in detecting pancreatic ductal adenocarcinoma (PDAC), and identify factors associated with false negatives (FN).

Methods: Patients diagnosed with PDAC in 2014-2015 were retrospectively identified by a cancer registry. CECTs performed during the diagnostic interval were retrospectively classified as true positive (TP), indeterminate or FN. Sensitivity TP/(TP+FN) was calculated for all CECTs and the following subgroups: protocol (uniphasic vs. biphasic); tumor size (≤ 2 cm vs. >2 cm); and resectability (potentially resectable vs. unresectable). Multivariate logistic regression was performed to assess which of the following factors were associated with FN: clinical suspicion of PDAC; size >2 cm; presence of metastases; protocol; isoattenuating tumor; and potentially resectable disease on imaging.

Results: 176 CECTs (127 uniphasic; 49 biphasic) in 154 patients (90 men, mean age 72±11 years) were included. Sensitivity was 125/149 (83.9%) overall, and 87/106 (82.1%) and 38/43 (88.4%) for uniphasic and biphasic protocols, respectively. Sensitivity was decreased for tumors ≤ 2 cm (45.4% vs. 90.6%), no liver metastases (78.0% vs. 95.9%), and potentially resectable disease (65.3% vs. 93.0%). Factors significantly associated with FN were clinical suspicion (OR, 0.24, 95% CI: 0.07-0.75), size>2 cm (OR, 0.10, 95% CI: 0.02-0.44), absence of liver metastases (OR, 4.94, 95% CI: 1.29-22.99) and potentially resectable disease (OR, 4.13, 95% CI: 1.07-16.65).

Conclusions: In our population, the overall sensitivity of CECT to detect PDAC is 83.9%, however this is substantially lower in several scenarios, including patients with potentially resectable disease. This finding has important implications for patient outcomes and efforts to maximize CECT sensitivity should be sought.

CLINICAL RELEVANCE STATEMENT: The sensitivity of CECT to detect PDAC is significantly decreased in the setting of sub-2 cm tumours and potentially resectable disease. A dedicated biphasic pancreatic CECT protocol has higher sensitivity and should be applied in patients with suspected pancreatic disease.

KEYWORDS: Pancreatic ductal carcinoma; computed tomography; sensitivity; delayed diagnosis

ABBREVIATIONS: CECT, contrast-enhanced computed tomography; PDAC, pancreatic ductal adenocarcinoma; PACS, Picture Archiving and Communication System; TP, true positive; IN, indeterminate; FN, false negative

KEY POINTS

1. The sensitivities of contrast-enhanced CT for detection of PDAC were 87/106 (82.1%) and 38/43 (88.4%) for uniphasic and biphasic protocols, respectively.
2. Sensitivity of contrast-enhanced CT was decreased for small tumors ≤ 2 cm (45.4% vs. 90.6%), if there were no liver metastases (78.0% vs. 95.9%), and with potentially resectable disease (65.3% vs. 93.0%).
3. Absence of liver metastases (OR, 4.94, 95% CI: 1.29-22.99) and potentially resectable disease (OR, 4.13, 95% CI: 1.07-16.65) were associated with a false negative (FN) CT result; suspicion of malignancy on the imaging requisition (OR,

0.24, 95% CI: 0.07-0.75) and size > 2 cm (OR, 0.10, 95% CI: 0.02-0.44) were negatively associated with FN.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is becoming an increasingly common cause of cancer-related death. The five-year survival of PDAC is the lowest of all solid cancers, ranging between 5-9% [1]. In the United States and Canada, pancreatic cancer is the fourth leading cause of cancer-related deaths [2; 3] and is projected to become the second leading cause of cancer-related death in the United States by 2030 [1; 4; 5].

Because PDAC is highly aggressive, early diagnosis is critical for optimal management and improving survival. Studies have shown that delays in the diagnosis of PDAC result in a significantly higher rate of advanced disease [6], lower rate of upfront surgery [7], and worse survival [8]. Because PDAC can be a challenge to diagnose clinically and is often first detected on imaging, the sensitivity of diagnostic imaging tests to detect PDAC is paramount.

In our region of Nova Scotia, Canada, survival of pancreatic cancer lags the national average [4]. In practice, we have observed challenges in detecting PDAC on contrast-enhanced computed tomography (CECT) examinations of the abdomen. Imaging manifestations of PDAC can be subtle and potentially missed, particularly if the mass is small, non-contour deforming or isoattenuating [9]. Imaging findings can also be misinterpreted for other pathology; for example, acute pancreatitis can mimic or mask PDAC [9; 10]. A PDAC that is missed or misinterpreted on imaging will delay diagnosis and can in turn impact resectability and survival. It is thus imperative for radiologists to be familiar with the imaging manifestations of PDAC, the sensitivity of abdominal imaging tests, and any potential factors that are associated with false negatives.

Given the lower survival of PDAC in our population and our observations in the diagnostic performance of CECT to detect PDAC, the primary objectives of this study were to assess the sensitivity of CECT to detect PDAC, and identify factors associated with a false negative result. Because diagnostic test results can impact patient outcomes, a secondary objective was to assess for differences in the mean diagnostic interval and mean survival according to CT test result.

METHODS

Study Design and Population

This retrospective population-based study was performed with approval from our institutional research ethics board, who waived the need for patient consent. Study subjects were patients consecutively diagnosed with PDAC from 1 January 2014 to 31 December 2015 as identified by the Nova Scotia Cancer Registry, and who underwent CECT imaging. A larger proportion of this patient population has been reported previously in a study that evaluated the implications of delays in the imaging diagnosis of PDAC [11], and derived pearls and pitfalls from missed or misinterpreted US, CT and MRI examinations [10]. The current study focused on the subset of patients that underwent CECT of the abdomen during the diagnostic interval (that is, after the patient presented to a healthcare professional for reasons felt related to PDAC, but before the definite diagnosis of PDAC was made). The date of diagnosis was established by the registry according to a hierarchical reference standard similar to the European Network of Cancer Registries [12]. CT examinations were excluded if they were obtained of another body part (eg. thorax), intravenous contrast material was not administered, or if a pancreatic abnormality was known at the time of interpretation (such as from a previous imaging examination).

Patient and CT Data Extraction

A Research Electronic Data Capture (REDCap) database hosted at Nova Scotia Health was used to record and store study data [13; 14]. The following data elements were imported from the cancer registry database: age at diagnosis; sex; weight; location of tumor as either proximal (head and uncinate process) or distal (neck, body, and tail); stage of disease (1-4, according to the American Joint Committee on Cancer Staging Manual, 8th edition); date of initial healthcare presentation and, if applicable, date of death. The diagnosis date was based on retrospective review of the electronic medical and imaging records, and corresponded to the date when the possibility of PDAC was first raised. The diagnosis was most often made on imaging, but may have included biopsy, brushings, or surgical resection. The Picture Archiving and Communication System (PACS) was searched for CTs performed during the diagnostic interval and included evaluation of the pancreas. The database was populated by two radiology residents (ML, JK) and validated by a fellowship-trained abdominal radiologist (AFC) with 6 years of post-fellowship experience.

For each CECT, technical and imaging data were recorded. Technical data included suspicion of cancer conveyed on the imaging requisition (such as unintentional weight loss, painless jaundice, or specific question of malignancy), CECT protocol (uniphasic portal venous phase (PVP) vs. biphasic pancreatic protocol), and amount of iodinated contrast administered intravenously, in mg of iodine (I). The biphasic protocol included a pancreatic parenchymal phase acquired 40-50s after initiation of contrast media injection, and a PVP obtained 70s after initiation of contrast media injection. CT scanners and protocols varied across the cohort. All CECTs included axial images and reformats in at least one long plane (coronal or sagittal). Slice thickness ranged from 2-5

mm for the uniphasic protocols and 1-3 mm for the biphasic protocols. The following imaging data were recorded: the greatest dimension of the tumor in any plane; enhancement of the tumor and pancreatic gland in PVP, using as large a region of interest as possible that did not include vessels, peripancreatic fat, or other confounder of attenuation such as artifacts; presence of liver metastases (multiple hypoenhancing liver lesions which were new if prior imaging studies were available, and which progressed if follow-up imaging was available); and whether the extent of disease was considered unresectable or resectable/borderline resectable (hereafter referred to as potentially resectable), as defined by NCCN guidelines [15].

The images and reports of CECT examinations were reviewed, and each examination was classified as true positive (TP), indeterminate (IN), or false negative (FN). CECT classifications were initially performed by ML and validated by AFC. Diagnostic criteria were according to established imaging findings of PDAC, summarized in Table 1 [9; 10; 16]. TPs corresponded to examinations where a pancreatic mass was identified and the suspicion of cancer was raised. IN examinations were those where the suspicion of cancer was not raised or equivocal, but follow-up imaging was recommended based on the presence of a pancreatic or extra-pancreatic abnormality, such as biliary obstruction or liver lesions. CECTs were classified as FN if manifestations of PDAC were evident, but no abnormality was reported and the patient's work-up was not advanced.

For each patient, the diagnostic interval was calculated as the difference in days between the date of first presentation to a healthcare professional for reasons considered related to PDAC, and the date of diagnosis. Survival was calculated as the difference between the date of diagnosis to the date of death or the census date (January 10, 2018).

Statistical Analysis

Statistical analysis was performed using Prism version 8.0.3 (GraphPad Software Inc., La Jolla, CA). Sensitivity was calculated according to the conventional method per STARD guidelines, TP/(TP+FN) [17]. Sensitivity was calculated for all CECTs and according to protocol (uniphasic and biphasic). For each protocol, sensitivity was also calculated for the following subgroups: tumors less than vs. at least 2 cm in greatest dimension; patients without vs. with liver metastases; and potentially resectable vs. unresectable disease.

Differences in the following continuous variables were assessed between TP, IN and FN CECTs (one-way ANOVA): age; weight; tumor size; and iodinated contrast media dose. Differences between subgroups were assessed with Tukey's multiple comparisons test. Chi-square was used to assess for associations between CECT result and the following categorical variables: CECT protocol; sex; tumor location; clinical suspicion of malignancy; potentially resectable disease; stage; and number of isoattenuating tumors. A tumor was considered isoattenuating if there was < 20 Hounsfield unit difference in attenuation between the tumor and pancreatic parenchyma in PVP [18]. Based on these analyses, factors that differed between TP and FN examinations were selected for inclusion in a multivariate logistic regression model of TP vs FN. The mean diagnostic interval and mean survival were compared between CECT examination results using one-way ANOVA.

RESULTS

Cohort

In our region, 257 patients were diagnosed with PDAC in 2014-2015 [11]. Of these, 214 patients underwent 275 CT examinations during the diagnostic interval. 99

CTs in 60 patients were excluded due to lack of intravenous contrast or non-dedicated abdominal CT (eg, CT thorax). The final cohort comprised 176 CECTs in 154 patients (90 men (58.4%), mean age 72 ± 11 years). There were 127 uniphasic PVP CECTs and 49 biphasic, pancreatic protocol CECTs.

Sensitivity

There were 125 TP, 27 IN, and 24 FN CECT examinations, resulting in an overall sensitivity of 83.9%. Examples of TP, IN and FN CECTs are provided in Figures 1-3, respectively. Shown in Table 2 are the sensitivity results according to CT protocol and specific subgroups. The sensitivities of uniphasic and biphasic CECT protocols were 82.1% and 88.4%, respectively. For tumors < 2 cm, the sensitivities dropped for uniphasic and biphasic protocols to 37.5% and 66.7%, respectively, although the sample size in these groups were small (n = 22 and n = 8, respectively). Sensitivity decreased slightly in patients without liver metastases, albeit less than that for sub-2 cm tumors: 74.3% and 86.7% for uniphasic and biphasic protocols, respectively. There was a substantial decrease in the sensitivity of uniphasic CECT in patients with resectable or potentially resectable disease (54.5%), however, the sensitivity of biphasic CECT remained relatively high in this subgroup (87.5%).

Patient and tumor characteristics

Patient and tumor characteristics are provided in Table 3 according to CECT result. There were no significant associations between CECT result and protocol ($p = 0.49$), sex ($p = 0.48$), tumor location ($p = 0.33$), or stage of disease ($p = 0.21$). The mean age of patients with IN CECTs was significantly lower than patients with TP CECTs ($p = 0.0003$), however, there was no significant difference in mean age between TP and FN

CECTs (p = 0.27) or IN and FN (p = 0.18). There was no statistically significant difference in mean weight between the three groups (p = 0.23) or in pairwise comparisons.

Mean tumor size was significantly larger in the TP group (4.1 cm) than in the IN (2.4 cm, p<0.0001) and FN (2.2 cm, p<0.0001) groups. There was a higher proportion of TP CECTs with a clinical suspicion of malignancy (67.2%) than in the IN (48.1%) and FN (37.5%) groups, however this did not reach statistical significance (p=0.053). A significantly higher proportion of TPs were associated with liver metastases (37.6% vs. 11.1% IN and 8.3% FN, p=0.001) and unresectable disease (74.4% vs. 33.3% IN and 29.2% FN, p<0.0001). The mean iodinated contrast media dose was lowest in the FN group, at 385 mg I / kg body weight. This was significantly lower than the IN group (459 mg I / kg, p = 0.02) but not significantly different from the TP group (427 mg I / kg, p = 0.14). The distribution of isoattenuating tumors was higher in the IN group (25.9%) than the TP (9.6%) and FN (8.3%) groups, however these differences were also not statistically significant (p = 0.05).

Multivariate logistic regression model

Based on results from Table 2 and Table 3, the following factors were included in a multivariable logistic regression model: clinical suspicion; CT protocol; size > 2 cm; absence of liver metastases; and potentially resectable disease. Shown in Table 4 are the corresponding odds ratios, 95% CIs and p-values. Factors that were negatively associated with FNs were a clinical suspicion of malignancy on the requisition (OR, 0.24, 95% CIs, 0.07 – 0.75) and size > 2 cm (OR, 0.10, 95% CI, 0.02-0.44). Factors that were positively associated with FNs were the absence of liver metastases (OR, 4.94, 95% CI, 1.29-22.99)

and resectable or borderline resectable disease (OR, 4.13, 95% CI, 1.07-16.65). CT protocol was not associated with FNs (OR, 3.48, 95% CIs, 0.81-17.69).

Differences in mean diagnostic interval and survival

A summary of time interval results is provided in Table 5. The mean diagnostic interval was significantly longer in the FN group (302.1 days) than the TP (84.3 days, $p<0.0001$) and IN (121.3 days, $p=0.009$) groups. However, mean survival of patients with FN CECT (165.5 days) was similar and not significantly different from that of patients with TP CECT (180.6 days, $p=0.947$).

DISCUSSION

In this study, we evaluated the sensitivity of CECT to diagnose PDAC as well as factors associated with FNs. A major finding from this study is that, although the overall sensitivity of CECT was 83.9%, sensitivity was substantially lower in some scenarios. In particular, the sensitivity of CECT to detect sub-2 cm tumors was poor (37.5% and 66.7% for uniphasic and biphasic CECTs, respectively). For uniphasic CECT, the sensitivity was also lower in patients without liver metastases (74.3%) and patients with potentially resectable disease (54.5%). On multivariate logistic regression, size < 2 cm, absence of liver metastases and resectable or potentially resectable disease were all significantly associated with FNs. These findings are problematic because patients with small and potentially resectable disease may be cured of their disease with an R0 resection. A delay in diagnosing a potentially resectable PDAC may result in the disease becoming inoperable and incurable; as such, measures to optimize the sensitivity of CECT and minimize FPs are essential to improving the survival of PDAC.

In our study, we did not find any corresponding improvement in mean survival between patients with TP and FN CECTs. This is likely because patients with TP CECTs had, on average, more advanced disease at the time of diagnosis than patients with FN CECTs. Patients in the FN group had a significantly smaller mean tumor size and a significantly smaller proportion of patients with liver metastases and unresectable disease. Nevertheless, our study did find that patients with FN CECTs had a mean diagnostic interval that was 218 days longer than patients with TP CECTs, and previous studies have conclusively shown that delays in the diagnosis of PDAC result in worse patient outcomes [6-8].

Previous studies have found the sensitivity of CECT to be similar to or higher than the present study: 17/20 (85%) [19]; 51-52/54 (94-96%) [20]; 23-27/28 (82-96%) [21]; 88/93 (95%) [22]; and 187/204 (91.7%) [23]. However, there are some important differences to note between these studies and the present study. First, these studies evaluated the sensitivity of a multiphasic CECT protocol [19-23], and not uniphasic CECT. One study evaluated the sensitivity of CECT for individual phases; although a lower sensitivity for the PVP was found (83/93, 89%), this was not significantly different from the full CECT protocol [22]. Second, when reported, patients were of substantially lower body weight. For example, the mean weights in Refs. [19] and [22] were 51 kg and 53 kg, respectively, as compared to 71.2 – 78.4 kg in our study (Table 3). For a fixed dose of iodinated contrast media, a higher body weight will result in less enhancement of abdominal viscera, and likely less conspicuity of tumors such as PDAC. Third, prior studies involved reinterpretation of CECT images by expert readers in the study design. In this study, we evaluated the historical performance of the index test. During our review, we found opportunities for radiologists to improve CECT interpretation; useful

resources on pearls and pitfalls of diagnosing PDAC on imaging are available elsewhere [9; 10].

Our finding of reduced CECT sensitivity to detect PDAC ≤ 2 cm is congruent with the literature. In a study of patients imaged from 1997-2000 using a quadriphasic CECT protocol, Bronstein et al. found a sensitivity of 14/18 (78%) [24]. In a prospective study by Kitano et al., the sensitivity of CECT for < 2 cm PDAC was 70.6% [23]. Clearly, size is an important factor impacting detection of PDAC, and techniques to improve conspicuity of small tumors on CECT should be sought. This includes use of submillimeter thin slices, review of multiplanar reformatted images, dual-energy CT, and careful evaluation of secondary signs of PDAC [16]. Secondary signs of PDAC include abrupt change in duct caliber, duct dilation or parenchymal atrophy upstream to the mass, and altered pancreatic contour (Table 1) [9; 10; 16]. There is early evidence that artificial intelligence may assist with detection of subtle PDAC as well [25]. Another significant factor identified by this study is a lack of clinical suspicion of malignancy on the CECT requisition, which was associated with FN. This highlights the importance for referring physicians to provide a thorough history on the imaging requisition, and may also reflect the cognitive biases that radiologists are susceptible to. An example of a cognitive bias is framing bias, which is the tendency to be influenced by how a question is asked or how a problem is presented. This can be avoided by seeking a more comprehensive history from the electronic medical record, or reviewing images prior to reading the indication [10; 26].

Some factors evaluated in our study were not associated with FN. The small sample of pancreatic protocol CECTs in the FN group (n=5) likely accounted for this being a non-significant factor in the multivariate logistic regression, given the clear improvement in sensitivity with the biphasic pancreas protocol. We believe radiologists

should routinely protocol CT requests of patients with suspected pancreatic or biliary disease with a biphasic pancreatic CECT, to help avoid a FN and to enable proper staging if a PDAC is identified. Unfortunately, the clinical presentation of PDAC is often vague and nonspecific, and uniphasic CECT is often performed first in patients with PDAC. We did not find significant differences between FN and TP CECTs with respect to contrast media dosing or proportion of isoattenuating tumors. On review of CECTs included in this study, however, we observed several PDAC masses with reduced conspicuity on CTs performed with low contrast media dosing, irrespective of test result. Technical specifications for CECT of the pancreas from the American Society of Abdominal Radiology [27] recommend using 125 mL of a contrast medium with high concentration (>300 mg I/L); however, for heavier patients this dose can be suboptimal. At our institution, we use a weight-based contrast dosing scheme of 500 mg iodine per kg of body weight for biphasic pancreatic CECT, as recommended by Fleischmann and Kamaya [28].

Our study has limitations. The retrospective study design and evaluation of a specific region and population may introduce selection biases. Classification of CECTs as TP, IN and FN was done with knowledge of the diagnosis of PDAC, which can introduce hindsight bias. The diagnostic work-up practices in our region are not necessarily the same as other regions, and this may limit generalizability. We only evaluated CECTs of patients with PDAC, and as such evaluated sensitivity but not other measures of diagnostic performance, such as specificity or accuracy. However, in our view sensitivity is paramount with respect to evaluating patients with suspected PDAC. Lastly, although we found that patients with FN results have significantly longer diagnostic intervals, association between a FN CECT and survival was confounded by earlier stage disease in the FN subgroup.

In conclusion, we found that the overall sensitivity of CECT in diagnosing PDAC was 83.9%. However, the sensitivity was lower for sub-2 cm tumors for both uniphasic and biphasic protocols, and for uniphasic CECT, sensitivity was also lower in the absence of liver metastases, and in resectable or potentially resectable disease. The sensitivity of CECT to detect PDAC is paramount to facilitate urgent referral, prompt management, and ultimately improved survival rates from this increasingly common cause of cancer-related death.

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FIGURE LEGENDS

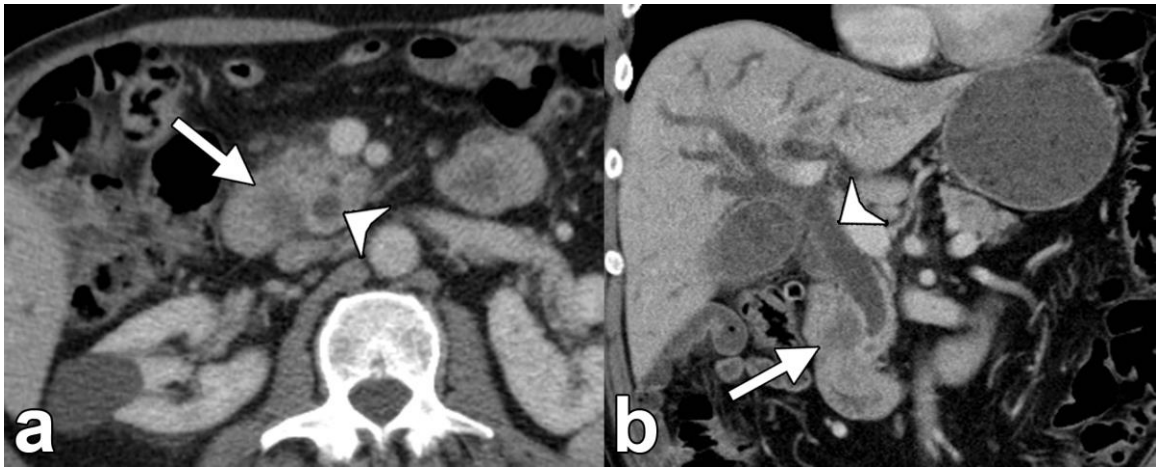

Figure 1. Example of a true positive CT examination. A 69 year-old man underwent uniphasic contrast-enhanced CT for evaluation of painless jaundice. (a) Axial and (b) coronal images show a 2.2 cm ill-defined hypoattenuating mass in the pancreatic head (arrows). There is obstruction of the common bile duct (arrowheads) and pancreatic duct (not shown). Imaging findings were interpreted as consistent with pancreatic adenocarcinoma.

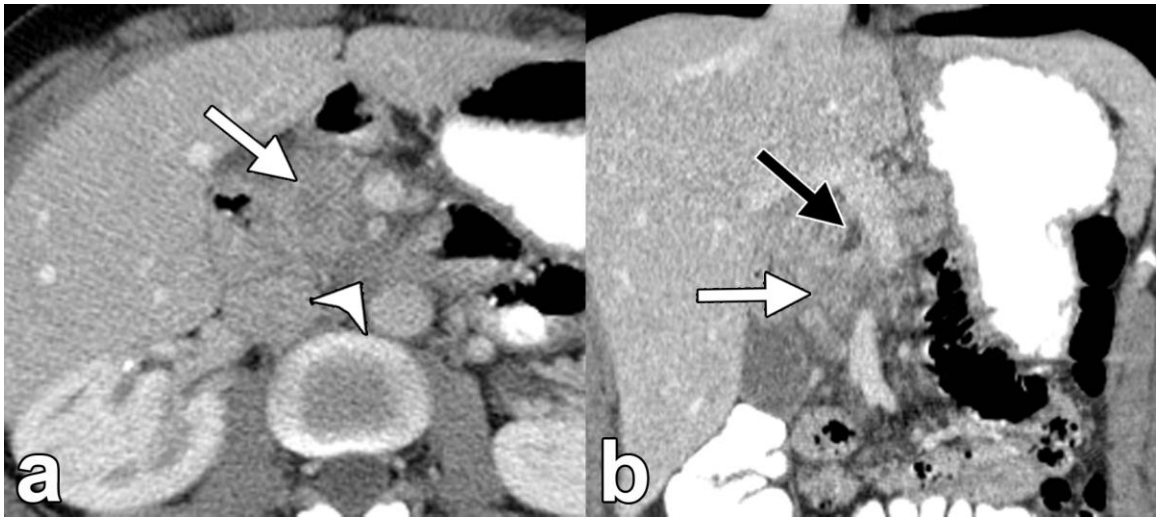

Figure 2. Example of an indeterminate CT examination. A 39 year-old woman underwent uniphasic contrast-enhanced CT for evaluation of abdominal pain for 2 weeks and elevated lipase. (a) Axial and (b) coronal images show an ill-defined hypoattenuating region in the pancreatic head (white arrows). There is effacement of fat surrounding the superior mesenteric vessels (arrowhead) and the pancreatic duct is dilated upstream to the pancreatic head (black arrow). Imaging findings were interpreted as possible pancreatitis, however, an MRI was recommended (not shown) and a pancreatic adenocarcinoma was diagnosed on that study.

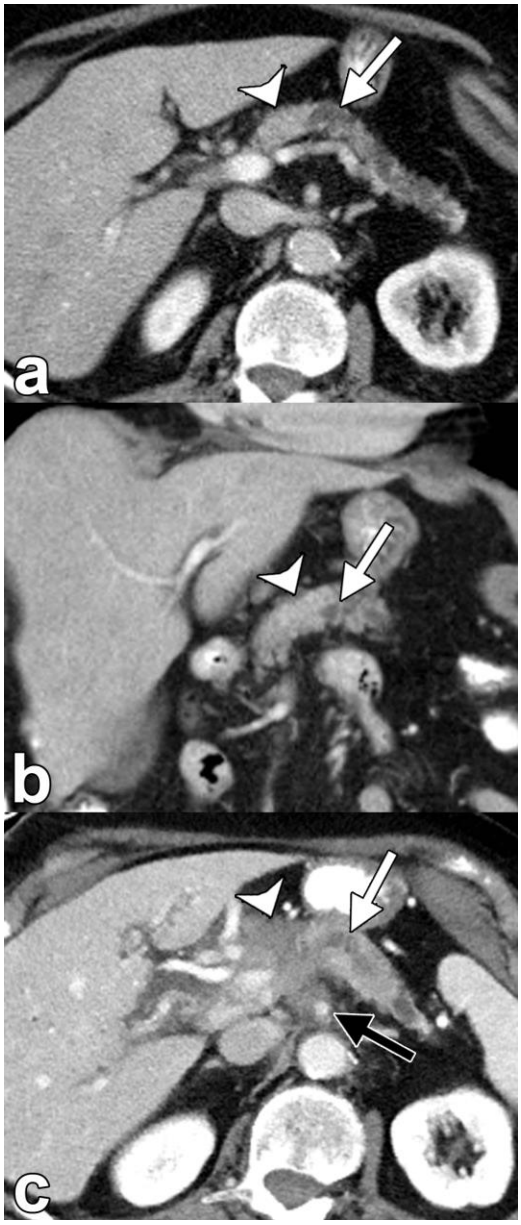

Figure 3. Example of a false negative CT examination. A 73 year-old woman presented to the Emergency department underwent uniphasic contrast-enhanced CT to evaluate vague abdominal tenderness and nausea. (a) Axial and (b) coronal images show sparing of atrophy in the pancreatic neck, with no contour deformity or altered attenuation (arrowheads). Upstream to this region, the pancreatic body and tail are atrophic and the main pancreatic duct is dilated (white arrows) with abrupt cutoff. Imaging findings were interpreted as a probable structure secondary to pancreatitis. (c) Axial contrast-enhanced CT was performed over 1 year later for right upper quadrant pain shows an ill-defined mass arising from the pancreatic neck (arrowhead), with worsening duct dilation (white arrow) and invasion of the superior mesenteric artery (black arrow).

TABLES

Table 1. Summary of CT Imaging findings of Pancreatic Ductal Adenocarcinoma

	Imaging Finding
Primary finding	• **Pancreatic mass**
Secondary pancreatic findings	• **Pancreatic and/or biliary duct dilation with abrupt cutoff upstream to the mass** • **Loss of fatty atrophy at site of mass** • **Parenchymal atrophy upstream to the mass** • **Contour deformity** • **Pancreatitis**
Secondary extra-pancreatic findings	• **Peripancreatic vascular invasion** • **Vascular thrombus, bland or tumoral** • **Collateral vessels** • **Metastatic disease (eg. liver, lymph nodes, peritoneum)** • **Ascites**

Table 2. Sensitivity of Uniphasic and Biphasic CT Protocols for Different Scenarios

	Uniphasic CT				Biphasic CT				All CT
	True Positive	**Indeterminate**	**False Negative**	**Sensitivity**	**True Positive**	**Indeterminate**	**False Negative**	**Sensitivity**	**Sensitivity**
All examinations	87	21	19	82.1%	38	6	5	88.4%	83.9%
Tumor ≤ 2 cm	6	6	10	37.5%	4	2	2	66.7%	45.4%
Tumor > 2 cm	81	15	9	90.0%	34	4	3	91.9%	90.6%
Liver metastases absent	52	19	18	74.3%	26	5	4	86.7%	78.0%
Liver metastases present	35	2	1	97.2%	12	1	1	92.3%	95.9%
Resectable or potentially resectable	18	14	15	54.5%	14	4	2	87.5%	65.3%
Unresectable	69	7	4	94.5%	24	2	3	88.9%	93.0%

Table 3. Characteristics of Patients, Tumors and CTs According to CT Result

	True Positive n = 125	Indeterminate n = 27	False Negative n = 24	p-value	Pairwise significant differences
No. of CT examinations					-
Uniphasic portal venous	87	21	19	0.49	
Pancreatic protocol	38	6	5		
Patient sex					-
M	72	16	17	0.48	
F	53	11	7		
Mean age (yrs)	72.9 ± 11	63.6 ± 12	69.1 ± 11	0.0004	TP vs. IN (p = 0.0003)
Mean weight (kg)*	73.6 ± 16	71.2 ± 13	78.4 ± 14	0.23	-
Location of tumor					-
Head/Uncinate	63	14	16	0.33	
Neck/Body/Tail	62	13	7		
Stage‡					
I / II / III	57	16	13	0.21	-
IV	59	9	9		
Mean tumor size (cm)	4.1 ± 2.2	2.4 ± 0.8	2.2 ± 1.1	< 0.0001	TP vs IN, p < 0.0001 TP vs. FN, p < 0.0001
Clinical suspicion of malignancy					-
Yes	84	13	9	0.053	
No	41	14	15		

Liver metastases					-
Present	47	3	2	0.001	
Absent	78	24	22		
Potentially resectable					-
Yes	32	18	17	< 0.0001	
No	93	9	7		
Mean iodinated contrast media dose (mg I / kg body weight)*	427 ± 100	459 ± 104	385 ± 79	0.028	IN vs FN, p = 0.021
Enhancement difference					
≥ 20 Hounsfield units	113	20	22	0.050	-
< 20 Hounsfield units	12	7	2		

* Patient weight was unavailable in 11 TPs, 0 INs and 4 FNs

‡ American Joint Committee on Cancer Staging Manual, 8th edition. Stage was unknown in 9 TPs, 2 INs and 2 FNs

Table 4. Multivariate logistic regression of factors associated with false positive CT examinations

Factor	Odds Ratio	95% confidence interval	p-value
Clinical suspicion	0.24	0.07 to 0.75	0.018*
CT protocol	3.48	0.81 to 17.69	0.146
Size > 2 cm	0.10	0.02 to 0.44	0.004*
Absence of liver metastases	4.94	1.29 to 22.99	0.027*
Resectable or borderline resectable disease	4.13	1.07 to 16.65	0.039*

Table 5. Mean Diagnostic Intervals and Survival According to CECT Examination Result

	True Positive	Indeterminate	False Negative	p-value	Pairwise comparison
Mean diagnostic interval (days)	84.3 ± 178	121.3 ± 140	302.1 ± 398	< 0.0001	TP vs. IN p=0.6994 TP vs. FN p<0.0001 IN vs. FN p=0.0091
Mean survival (days) ‡	180.6 ± 195	365.6 ± 357	165.5 ± 131	0.0008	TP vs. IN p=0.0007 TP vs. FN p=0.9471 IN vs. FN p=0.0052

† In patients who underwent multiple CECTs, results are based on the first-time examination.

CECT, contrast-enhanced computed tomography; TP, true positive; IN, indeterminate; FN, false negative