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Undetected pancreatic carcinoma: Retrospective analysis of missed findings at computed tomography

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ABSTRACT

Purpose: Our purpose was to retrospectively investigate whether prediagnostic CT scan may show suggestive findings of early pancreatic cancer.
Material and Methods: We searched our radiology and surgery database to identify all patients who had a CT diagnosis of pancreatic ductal adenocarcinoma at our institution in a three-year span and reviewed our PACS system to search whether any of these patients had CT or MR examinations performed before the diagnosis of pancreatic cancer was made. We therefore looked for the presence of pancreatic duct dilatation and/or interruption, distal parenchymal atrophy, contour abnormality and focal hypoattenuating lesion in the prediagnostic CT scans.
Results: Three patients had performed previous imaging examinations showing findings suspicious for pancreatic cancer 1-9 months earlier than a diagnostic CT was performed. A focal attenuation difference, followed by contour abnormality and upstream pancreatic duct dilatation were the most encountered findings, while upstream pancreatic parenchymal atrophy was encountered in one patient.
Conclusions: Prediagnostic CT can detect findings suggestive of indolent early pancreatic cancers. The most common suggestive findings are focal hypoattenuating lesion and pancreatic duct dilatation and/or interruption.

KEY WORDS
pancreatic neoplasms; multidetector computed tomography; early diagnosis/indolent tumour

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1. Introduction

Pancreatic ductal adenocarcinoma (PDA) has a dismal prognosis, being the 4th leading deadly cancer with an overall 5-year survival rate of 7% [1]. Only less than 20% of patients with PDA are diagnosed early enough to allow surgical resection, which is to date the only curative therapy [1, 2].

CT has been considered for years the most accurate imaging modality for diagnosis and staging of PDA. The sensitivity of CT for the detection of small PDA ranges from 63% to 85% [3-5]. Early PDA is usually not associated with any signs or symptoms; thus, imaging has a prominent role in its prompt diagnosis at asymptomatic stages [6, 7]. Indeed, as the use of CT increases, there is higher probability of tumour detection at early stages. Even though, perceptual errors [8, 9], inadequate protocol design (i.e. lack of pancreatic phase) or inadequate image acquisition (i.e. low mA that could lead to noiser images) may all lead to missed cancer lesions [10].

Focal hypoattenuating area, pancreatic duct dilatation, interruption of the pancreatic duct and distal parenchymal atrophy on CT images are useful findings for the early detection of PDA; among these, the presence of a focal hypoattenuating area is most frequently encountered [3, 6]. However, when the study is performed for reasons other than pancreatic disease and one or more of these key imaging features are incidentally present, even experienced abdominal radiologists may sometime miss early PDA on CT [3, 6].

The purpose of our study was to retrospectively investigate the imaging findings of PDA that were prospectively missed in patients who had CT for reasons other than pancreatic disease.

2. Material and methods

We searched our hospital database for patients who had a CT diagnosis of PDA at our institution in a three-year span. CT criteria for a diagnosis of PDA were the presence of a hypoattenuating mass seen in the pancreatic phase, with or without i) pancreatic duct upstream dilatation, ii) upstream pancreatic atrophy and iii) mesenteric vessels abutment or encasement. We reviewed our PACS system and found three patients who had undergone at least one CT before the diagnosis of PDA was made and in whom we were able to identify early features of the disease that had been missed by the radiologist in our Institution. The medical data and imaging findings were retrospectively reviewed. Due to its retrospective nature, our institutional ethics committee did not require approval for this study, and patient informed consent was waived.

2.1 Imaging technique

Prediagnostic and diagnostic CT had been performed either with a 16-row multidetector CT scanner (G.E., Milwaukee, WI) or a 128-row multidetector CT scanner (Somatom Definition AS + Siemens 128, Siemens, Medical Solution, Erlangen, Germany). Imaging protocol acquisition included a non-enhanced phase and a portal venous phase at 80 seconds from intravenous iodinated contrast agent injection; according to the clinical context, an arterial phase and/or a delayed phase after injection had been acquired. CT parameters of prediagnostic and diagnostic CT scans are reported in **Table 1**.

2.2 Imaging analysis

Images were retrospectively reviewed in consensus by an abdominal radiologist (G.B.) and a radiology resident (F.V.) with 20- and 4- year-experience respectively. CT or MR scans in which the PDA had been reported by the radiologist are named "diagnostic CT/MR". CT scans performed before the diagnostic one and in which the observation could be (but was not) noted are named "prediagnostic CT". Reviewers recorded the presence or absence on prediagnostic CT of the following imaging features: Focal hypoattenuating lesion, upstream pancreatic duct dilatation and/or interruption, upstream parenchymal atrophy and contour abnormality.

Focal hypoattenuating lesion was defined as an area of unequivocally lower density compared to the normal parenchyma. Upstream pancreatic duct dilatation was noted if the duct was dilated >3 mm. Upstream parenchymal atrophy was defined as atrophy of pancreatic parenchyma distal to the lesion or disproportional atrophy if there was no pancreatic focal lesion. Contour abnormality was defined as a loss of the normal pancreatic lobulation. CT findings were considered present if they were identified by both reviewers in consensus.

3. Results

Among those patients who had a diagnosis of PDA and had undergone a diagnostic CT in our Radiology Department, three patients had performed at least one prediagnostic CT in which imaging findings suspicious for tumour were detectable. A total of seven CT and one MR scans were evaluated in these three patients. The reason for the examinations were oncologic follow-up in two patients and liver and chronic liver disease in one patient.

Patient 1 was a 54-year-old female operated in 2009 for right adnexal carcinoma, sigmoid adenocarcinoma, co-

Table 1. CT parameters of prediagnostic CT

	CT scanner	Type of iodinated contrast medium	Enhancement phase
Patient 1 -September 2014	128 Somatom	Iopromide 370 mg/ml	Arterial Portal Delayed
-November 2014 -February 2015	16 GE 16 GE	Iomeprolo 400 mg/ml Iopromide 370 mg/ml	Portal Portal Delayed
Patient 2 -October 2012	128 Somatom	Not recorded	Arterial Portal Delayed
Patient 3 -March 2013	128 Somatom	Iomeprolo 400 mg/ml	Arterial Portal Delayed
-July 2013	128 Somatom	Ioexolo 350 mg/ml	Portal Delayed

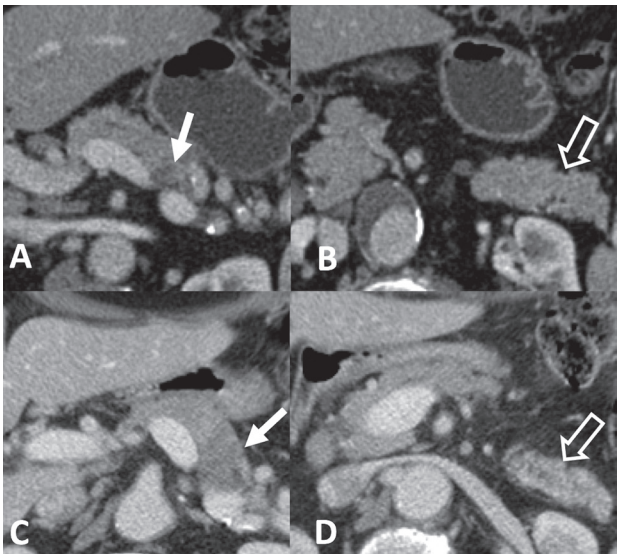

Fig. 1. *A and B. CT scans in the portal venous phase performed in a 70-year-old man with splenomegaly and chronic hepatititis C (patient 2). Prediagnostic CT scan (A and B) shows a focal hypoattenuating lesion (arrow) in the posterior part of the body of the pancreas with contour abnormality. Note normal morphology of the distal pancreatic parenchyma (open arrow). Diagnostic CT scan performed nine months later (C and D) shows a focal hypoattenuating lesion in the junction of the body and tail (arrow), with loss of normal lobulation of the pancreatic contour and upstream pancreatic duct dilatation along with atrophy of upstream pancreatic parenchyma (open arrow)*

lonic metastases to the left adnexus and lymph nodes and in 2012 for metastases to the abdominal muscles and iliac lymph nodes and subjected to chemotherapy in the meantime. For this oncologic history, the patient was followed-up with CT scans since 2009. On the CT scan performed in February 2015 the radiologist reported the appearance of a 1.5 cm lesion in the junction of the body and tail of the pancreas associated with atrophy of the upstream tail and minimal dilatation of the upstream pancreatic duct.

Patient 2 was a 70-year-old male referred by the Gastroenterology Unit for splenomegaly and history of chronic hepatitis C. **Fig. 1** shows the prediagnostic (parts A and B) and diagnostic (parts C and D) CT scans of this patient. On the diagnostic CT scan performed in July 2013 the radiologist reported a 3 cm lesion in the junction of the body and tail of the pancreas (**Fig. 1**) with associated atrophy of the upstream tail.

Patient 3 was a 69-year-old male operated for sigmoid carcinoma in January 2013 and followed up with CT and MR because of liver metastases. On MR the radiologist reported the appearance of a hypoattenuating lesion on T1 in the body/tail of the pancreas (**Fig. 2**) with atrophy of the upstream tail.

In all three cases a minimum of one prediagnostic CT in which the lesion was judged as retrospectively detectable by the reviewers of this study was available. The prediagnostic CTs had been performed 3 months and 5 months earlier than diagnostic CT for patient 1, 9 months earlier for patient 2 and 2 months and 6 months earlier for patient 3.

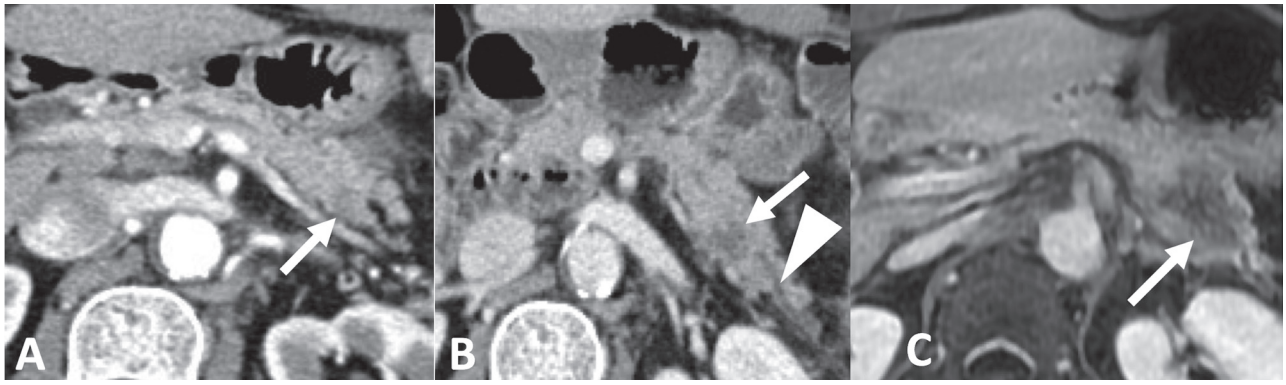

Fig. 2 A-C. *CT and MR scans in the portal venous phase performed in a 69-year-old man, with history of operated sigmoid carcinoma (patient 3). Prediagnostic CT scan (A) shows a focal mildly hypoattenuating lesion in the posterior part of the junction of the body tail of the pancreas (arrow). Prediagnostic CT scan performed four months later (B) shows a lower density of the focal lesion (arrow), upstream parenchymal atrophy, pancreatic contour abnormality with loss of normal lobulation and upstream pancreatic duct dilatation (arrowhead). (C) Diagnostic MR scan performed one month later shows on portal venous phase T1-weighted image a focal hypointense lesion (arrow) in the body /tail of the pancreas with loss of the normal contour lobulation; distal parenchymal atrophy was also present (not shown)*

Concerning patient 1, on the prediagnostic CT scan performed in September 2014, a focal hypoattenuating lesion of 0.4 cm of maximum short axis was detectable, while upstream pancreatic duct, dilatation, loss of lobulation and upstream parenchymal atrophy were not present. The same findings were noted in the second emergency pre diagnostic CT scan performed in November 2014 due to clinical suspicion of pancreatitis and the radiologist reported just the presence of pancreatic duct dilatation in the tail, but the focal hypoattenuating lesion and the loss of parenchymal lobulation were not reported; however, the focal hypoattenuating lesion was less easily detectable due to the presence of hypoattenuation of the distal pancreatic parenchyma.

The images related to this patient have been recently published in a review on pitfalls in pancreatic imaging [11].

Concerning patient 2, on the prediagnostic CT scan performed in October 2012, a focal hypoattenuating lesion of 0.5 cm in the body of the pancreas was detectable (**Fig. 1**), without any upstream pancreatic duct dilatation, distal parenchymal atrophy or loss of lobulation; however, a minimal contour abnormality was present due to the location of the lesion.

Concerning patient 3, there were two prediagnostic CT scans. In the first, performed in March 2013, there was a focal hypoattenuating lesion in the tail of the pancreas (**Fig. 2**). Although low density was not so marked, the presence of upstream parenchymal atrophy could have helped in the recognition of the hypoattenuating lesion. In July 2013 the second prediagnostic CT scan showed lower density of the lesion, increase of the upstream parenchymal atrophy and the appearance of pancreatic contour abnormality and upstream pancreatic duct dilatation.

Therefore, regarding the radiological signs detected on prediagnostic CT scans (**Table 2**), a focal hypoattenuating lesion was detectable in all patients and in all prediagnostic CT scan. Upstream pancreatic dilatation and contour abnormality were detectable just in the first and third patient who had been subjected to a second CT scan respectively three months and one month earlier than diagnostic CT scan. Upstream pancreatic parenchyma atrophy was detectable just in the third patient in the prediagnostic CT scan performed one month earlier than the diagnostic CT scan.

4. Discussion

We report on three cases of missed small PDA that in retrospect could have been detected on CT performed 1-9 months before a diagnosis was made. Our results are similar to those reported by Gangi et al. [6], in which definite or suspicious CT findings for PDA were noted respectively in 50% of the scans obtained 2-6 and 6-18 months before the clinical diagnosis.

In our three patients, despite a delayed diagnosis of up to 9 months and a consequent marked dimensional increase, PDA remained asymptomatic in all cases, possibly due to the location in the body-tail of the pancreas rather than in the head.

In the last twenty years, the wider use of CT and MRI

Table 2. Radiological signs encountered in the prediagnostic CT scans in the three patients

	Focal hypoattenuating lesion	Upstream pancreatic duct dilatation	Upstream pancreatic parenchyma atrophy	Contour abnormality
Patient 1				
-September 2014	x	-	-	-
-November 2014	x	x	-	x
Patient 2				
--October 2012	x	-	-	-
Patient 3				
-March 2013	x	-	x	-
-July 2013	x	x	x	x

has led to incidental detection of many lesions, including malignancies. Among these imaging techniques, CT is the most widely used, and its sensitivity in the early diagnosis of PDA is positively related to tumour size [4-6].

Our study shows that a focal hypoattenuating lesion was the most common missed finding, and this is in accordance with previous reports [3, 7]. Other missed signs that could have suggested a diagnosis of PDA were contour abnormality and upstream pancreatic duct dilatation, both encountered in 2 of our 3 patients. These two latter findings, however, were not present even in retrospect in the first prediagnostic CT scans performed 5 months earlier than the diagnostic CT in the two patients.

Both contour abnormality and upstream pancreatic duct dilatation were present only on the last prediagnostic CT scan performed 3 months and 2 months earlier respectively, thus indicating that these can be delayed findings on prediagnostic CT compared to focal attenuation difference.

Focal hypoattenuation, pancreatic duct dilatation and contour abnormality are thus important suggestive findings of early PDA. However, in the work by Ahn et al. [3], none of them proved to be useful in the differentiation of PDA from chronic pancreatitis. Moreover, PDA may be accompanied by clinical symptoms and radiological signs of chronic pancreatitis as for patient 1, thus making diagnosis on CT more difficult.

Upstream pancreatic parenchymal atrophy was encountered only in patient 3 in both prediagnostic CT examinations. Although being more uncommon as a finding of early PDA compared to focal hypoattenuation and pancreatic duct dilatation/interruption, distal parenchymal atrophy is the only finding whose presence allows a definitive differentiation between PDA and chronic pancreatitis, showing a specificity of 96% in the diagnosis of PDA, although sensitivity is only 45% [3]. The presence of upstream parenchymal atrophy should suggest the presence of an underlying focal primary neoplasm, even when the lesion itself is not clearly detectable. Moreover, the presence of pancreatic atrophy at preoperative CT has been associated with poorer prognosis [12].

Although less performed, more expensive and time consuming than CT, MR may provide some useful diagnostic clues for the detection of early PDA and for the differential diagnosis between PDA and chronic pancreatitis [7, 13].

The usefulness of MR for PDA detection was demonstrated in patient 3, in whom a CT scan performed just 2 months earlier had not raised the suspicion of a tumour to the radiologist. Although a liver study had been acquired, MR images clearly depicted the loss of the hyperintense signal on T1 of the normal pancreatic parenchyma due to the PDA. The normal hyperintensity of normal pancreatic parenchyma is related to the presence of proteins and manganese within it; the loss of this hyperintensity in case of PDA is due to the presence of an abundant, dense fibroblastic stroma with a decreased number of vessels within PDA. However, all the four typical features of PDA were already retrospectively detectable also on the prediagnostic CT performed one month before MR.

The diagnostic "discrepancies" between the prospective report and the retrospective review of images may have been related to different causes, such as perceptual errors or satisfaction of search, related to the temptation to not actively pursue the detection of new lesions in patients with multiple pre-existing lesions that need to be compared

in oncologic follow-up examinations. Moreover, it must be considered that the majority of these exams were performed for different reasons and thus a dedicated pancreas protocol was not acquired (absence of a pancreatic phase) [8, 9, 14]. In two of our three patients there were more than one prediagnostic CT scans in which the imaging findings were not detected, although this is consistent with previous studies that showed that undetected findings of PDA were retrospectively visible in more than one prediagnostic imaging examinations [3, 6, 7]. However, considering the aggressiveness of PDA and its rapid growth as demonstrated in these two patients, a careful evaluation of minimal radiological changes is advisable. Limitations of the present study are its retrospective nature and the small number of patients.

In conclusion, prediagnostic CT provides early imaging findings that should raise the suspicion of PDA. The presence of a focal hypoattenuating lesion is the most common finding, although it lacks specificity, while distal pancreatic parenchyma atrophy is highly specific for PDA, although it lacks sensitivity. When one or more of these signs are encountered, they must be reported and a dedicated study should be performed. **R**

Conflict of interest:
The authors declared no conflicts of interest.

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