Imaging of early pancreatic cancer on multidetector row helical computed tomography

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ABSTRACT. Early pancreatic cancer is small and limited to the pancreas. In contrast, small pancreatic cancer may include peripancreatic vasculature or metastasis involvement. This study evaluates images of early pancreatic cancer on multidetector CT (MDCT) using contrast-enhanced multiphasic imaging, and post-processed pancreatic duct images. CT findings and pathological features were analysed in eight patients with early pancreatic cancer. Pathological evaluation included location, size and histological grading of the tumour. MDCT evaluation covered the maximum diameter of the main pancreatic duct (MPD), stenosis or obstruction of the MPD, loss of normal lobar texture and associated pancreatitis. Attenuation differences between normal pancreatic parenchyma and the tumour (AD–PT) were also measured. Focal stenosis or obstruction of the MPD with dilatation of the distal MPD was demonstrated in all patients. Associated pancreatitis occurred in six patients with tumours measuring 12 mm or greater. Loss of normal lobar texture was recognised in four cases with the tumour measuring 14 mm or greater. Statistically, low-attenuated lesions and high-attenuated lesions differed with respect to the tumour size ($p < 0.01$), and a positive relationship was demonstrated between the tumour size and AD–PT ($r = 0.84$). In seven cases, AD–PT is higher during the arterial phase than the pancreatic phase. Early pancreatic cancer appears as low attenuation on early phase, and as high- to iso-attenuation during the pancreatic and delayed phases in respect to the tumour size. Focal stenosis or obstruction of the MPD with dilatation of the distal MPD observed on curved reformation imaging seems important in the diagnosis of early pancreatic cancer.

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It is well known that pancreatic cancer is rarely cured and often fatal. Surgical resection is currently the only potentially curative treatment for pancreatic carcinoma, and detection of pancreatic cancer at an early stage is very important for increasing the resectability of the tumour and improving prognosis. Stage I pancreatic cancer, or early pancreatic cancer, is defined as a tumour smaller than 2 cm by histological measurement, limited to the pancreas without invasion to the peripancreatic vasculature, lymph node metastasis or distant metastasis [1]. It is generally known that the smaller the tumour size and the earlier the clinical stage, the better the prognosis. Small pancreatic cancer is defined as a tumour smaller than 2 cm with or without invasion to the peripancreatic vasculature or metastasis.

Contrast-enhanced helical CT has facilitated the detection and staging of pancreatic cancer and is accepted as one of the most effective imaging techniques for the diagnosis of pancreatic cancer [2–10]. Current multidetector row helical CT (MDCT) can provide imaging details of pancreatic lesions, and some studies have reported on the imaging of small pancreatic cancer

[4], but limited data are available comparing small and early pancreatic cancer.

In the present retrospective study, we evaluated images of small and early pancreatic cancer on MDCT using contrast-enhanced multiphasic imaging and post-processed pancreatic duct images and compared them with the pathological findings of surgical specimens.

Methods and materials

Patients

CT findings and pathological features were analysed in eight patients (four males and four females; age range 48–78 years; mean 60 years) with early pancreatic cancer between November 2003 and November 2008. Eight patients were retrospectively selected from pathological records in our institute, where early pancreatic cancer had been proved by post-surgery histological examination. All patients presented symptoms of abdominal discomfort or pain, and clinical and radiological examination, including ultrasonography or routinely performed abdominal CT with or without a contrast study, showed some abnormality of the pancreas. All patients presented no symptoms of cardiac insufficiency or renal failure. All patients underwent pre-operative

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MDCT at our institution within three weeks prior to surgery. All the lesions ($n=8$) were resected by either distal pancreatectomy ($n=4$) or pylorus-preserving pancreaticoduodenectomy ($n=4$). The type of resection performed was determined on the basis of the location of the pancreatic lesions on CT.

CT technique

MDCT was performed using a multidetector row 8-channel helical CT unit (Light speed QX/I; GE Medical System, Milwaukee, WI). Initially non-enhanced images of the upper abdomen were obtained using 7-mm collimation. A contrast medium (Iohexol; Daiichi-Sankyo, Tokyo, Japan) of 2 ml kg^{-1} of the patient's body weight was injected at a concentration of 300 mgI ml^{-1} into an antecubital vein for 30 s. The injection rate

ranged from 3.0 to 4.6 ml s^{-1} and was adjusted according to the total volume of the contrast medium. A three-phase contrast study was performed by 1.25-mm collimation through the pancreas with a breath-held acquisition. Arterial-phase imaging was performed 25 s after initiating the administration of the IV contrast medium. Pancreatic and delayed-phase imaging were performed 60 s and 120 s, respectively, after initiating administration of the IV contrast medium. The pancreatic-phase images reconstructed with 1.25 mm thickness at 0.625 or 1.25 mm spacing were subsequently post-processed at a workstation (ADW 4; GE Medical System). Pancreatic duct images on arterial and pancreatic phases were obtained using curved reformation with a slab thickness of 2 mm by tracing the entire course of the main pancreatic duct (MPD) by interactively placing a cursor on a stack of axial, sagittal, coronal or oblique sections.

(a)

(b)

(c)

Figure 1. 60-year-old woman with early pancreatic carcinoma measuring 8 mm (Case 1). (a) Axial image during the pancreatic phase shows a high attenuation tumour at the site of MPD stenosis (arrow). Curved reformation images during the arterial phase (b) and pancreatic phase (c) show the entire course of the MPD, clearly demonstrating focal stenosis and distal dilatation of the MPD. The tumour at the site of MPD stenosis presented as a high- to iso-attenuated lesion during pancreatic-phase imaging (arrow).

Analysis of imaging and pathological findings

Pathological findings were evaluated with respect to location, size and histological grading of the tumour. Laboratory data, including serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), were measured in all patients.

CT findings were evaluated from axial images and two-dimensional (2D) reformation images on the workstation, and were interpreted separately by two radiologists. The workstation allowed the reviewers to edit CT volume data to create optimal reformatted images. In cases of disagreement, final decisions were reached by consensus.

MDCT findings were evaluated focusing on the maximum diameter of the MPD, stenosis or obstruction

of the MPD with dilatation of the distal MPD, loss of normal lobar texture at the site of the lesion, associated pancreatitis, and atrophic changes in the pancreatic parenchyma. Dilation of the MPD is defined as a diameter of the MPD greater than 5 mm. Associated pancreatitis is defined as the presence of a contrast between the areas of pancreatic parenchyma proximal and distal to the site of the MPD obstruction during arterial or pancreatic-phase imaging.

Attenuation of the tumour and normal pancreatic parenchyma were measured on non-enhanced arterial, pancreatic and delayed-phase imaging. Attenuation differences between normal pancreatic parenchyma and the tumour (AD-PT) were also measured. (AD-PT = attenuation of pancreatic parenchyma - attenuation of tumour (HU)). If it was difficult to identify the tumour

(a)

(b)

(c)

Figure 2. 55-year-old woman with early pancreatic carcinoma measuring 10 mm (Case 2). (a) Axial image during pancreatic phase shows a high- to iso-attenuation tumour at the site of MPD stenosis (arrow). Curved reformation images on axial base (b) and coronal base (c) during the pancreatic phase show the entire course of MPD, and focal stenosis and distal dilatation of the MPD are clearly demonstrated. The tumour at the site of MPD stenosis appeared as high- to iso-attenuated lesion during the pancreatic phase (arrows).

on axial images, the region of interest (ROI) was defined at the proximal portion adjacent to the MPD stenosis on the workstation by interactively placing a cursor on a stack of axial and 2D reformation pancreatic duct images.

Statistical methods

Cohen's κ coefficient was calculated for interobserver agreement for categorical diagnosis with respect to the presence of stenosis or obstruction of the MPD with dilatation of the distal MPD, loss of normal lobar texture at the site of the lesion, associated pancreatitis and atrophic changes in the pancreatic parenchyma. Measured values of the diameter of MPD or AD-PT by two radiologists were averaged.

The relationship between the enhancement pattern of the tumour and tumour size was evaluated. Correlation between AD-PT during pancreatic-phase imaging and tumour size was also evaluated using the Pearson product-moment correlation coefficient (r). With respect to the tumour size, we applied the Wilcoxon test to evaluate the statistical difference between the low-attenuated lesions and the high-attenuated lesions during the pancreatic phase.

All statistical analyses were performed using SAS (ver. 9.1: SAS Institute, Cary, NC).

Results

Pathological examination of the eight patients showed early pancreatic cancer with the tumour diameter ranging from 8 mm to 19 mm (mean 13.5 ± 3.8 mm).

Tumours were located in the pancreatic head in five patients (well-differentiated adenocarcinoma, $n=1$;

moderately-differentiated adenocarcinoma, $n=4$) and in the body in three patients (well-differentiated adenocarcinoma, $n=1$; moderately differentiated adenocarcinoma, $n=1$; poorly differentiated adenocarcinoma, $n=1$) (Figures 1–4). Only one patient had abnormal elevation of tumour markers (Case 7): elevated serum CA19-9 (Table 1).

Focal stenosis or obstruction of the MPD with dilatation of the distal MPD was demonstrated in all patients. The maximum diameter of the distal MPD ranged from 6.0 mm to 7.0 mm (mean diameter 6.6 ± 0.5 mm). Evidence of associated pancreatitis was demonstrated in six patients with the tumours measuring 12 mm or greater, and two of them showed atrophic change in the pancreatic parenchyma. Loss of normal lobar texture at the site of the lesion was observed in four cases with the tumour measuring 14 mm or more (Table 2).

Mean values of AD-PT in all eight patients were 5.7 ± 3.9 HU on non-enhanced images, 22.4 ± 15.3 HU during arterial phase, 6.5 ± 21.8 HU during pancreatic phase and -13.0 ± 21.1 HU during delayed-phase imaging.

During pancreatic-phase imaging, the tumours appeared as low-attenuated lesions in the four cases with the tumours ranging from 14 mm to 19 mm in diameter (mean 16.5 ± 2.4 mm), and as high-attenuated lesions in the four cases with the tumours ranging from 8 mm to 12 mm in diameter (mean 10.5 ± 1.9 mm) (Table 3) (Figure 5). There was a statistical difference between the low-attenuated lesions and the high-attenuated lesions with respect to the tumour size ($p < 0.01$ using the Wilcoxon test), and there was a positive relationship between tumour size and AD-PT value ($r = 0.84$) (Figure 6).

In seven cases, AD-PT is higher during the arterial phase than during the pancreatic phase.

(a)

(b)

Figure 3. 72-year-old woman with early pancreatic carcinoma measuring 18 mm (Case 6). Axial image (a) and curved reformation image (b) during the arterial phase show a low-attenuation tumour with loss of normal lobar texture at the site of MPD obstruction (arrow) and distal dilatation of the MPD.

Figure 4. 50-year-old man with early pancreatic carcinoma measuring 19 mm (Case 7). Curved reformation image shows associated pancreatitis revealed as a contrast between the areas of the pancreatic parenchyma proximal and distal to the site of MPD obstruction (arrow) during the arterial phase (a), and shows a low-attenuation tumour with loss of normal lobal texture at the site of MPD obstruction (arrow) during the pancreatic phase (b).

Cohen's κ -value calculated for interobserver agreement for categorical diagnosis was 1, indicating perfect interobserver agreement.

Discussion

It is well known that the prognosis of pancreatic cancer is extremely poor, even when treated with radical surgery. The overall 5-year survival rate in pancreatic cancer following surgical intervention is around 10% [11, 12].

Although pancreatic cancer is rarely cured, it has a good prognosis if resected when the tumour is small and limited to the pancreas. Ariyama et al [13] showed a 100% 5-year post-operative survival rate for patients whose tumours were smaller than 1 cm and limited to the intraductal epithelium without parenchymal, vascular, perineural or lymphatic invasion. Shimizu et al [14] reported that the cumulative 3- and 5-year survival rates for small pancreatic carcinoma (<2 cm) were 88.9% and 59.3%, respectively. The rates for patients with pancreatic carcinoma (>2 cm) were significantly lower (18.7% and 9.3% at 3 years and 5 years, respectively) [14].

Maximal pancreatic enhancement is essential for the detection of pancreatic carcinoma, and optimal enhancement of peripancreatic vessels is essential for the evaluation of peripancreatic vascular involvement. Several reports have emphasised the importance of pancreatic-phase imaging (40–70 s after infusion of IV contrast material at 3 ml s^{-1}) for the detection of pancreatic tumours and evaluation of peripancreatic vasculature involvement [7–9]. Lu et al [7] explained that, compared with hepatic-phase imaging, pancreatic-phase acquisition provides significantly better pancreatic, arterial and portal venous enhancement with improved tumour–pancreatic contrast. Boland et al [8] reported that contrast between pancreatic tumours and normal pancreas is increased during pancreatic-phase imaging because of superior enhancement of normal pancreatic parenchyma and reduced enhancement of the tumour. McNulty et al [2] reported that a combination of pancreatic parenchymal-phase and portal venous-phase imaging is sufficient for the detection of pancreatic adenocarcinoma because it provides maximal pancreatic parenchymal and peripancreatic vascular enhancement. In this study, contrast between pancreatic tumours and

Table 1. Pathological findings of the tumour and tumour markers of the seven patients

Case	Location	Size of the tumour (mm)	Histological grading	Elevation of tumour marker
1	Head	8	G2	(–)
2	Head	10	G2	(–)
3	Body	12	G1	(–)
4	Head	12	G1	(–)
5	Body	14	G2	(–)
6	Head	15	G2	(–)
7	Body	18	G3	(–)
8	Head	19	G2	(+) ^a

G1, well-differentiated adenocarcinoma; G2, moderately differentiated adenocarcinoma; G3, poorly differentiated adenocarcinoma.

^aSerum CA19-9 level was 43.3 IU ml^{-1} (normal value <37).

Table 2. Imaging findings of the tumour and pancreas

Case	Stenosis of MPD with dilatation of distal MPD	Diameter of MPD (mm)	Loss of normal lobar texture	Associated pancreatitis	Atrophic change
1	(+)	6	(-)	(-)	(-)
2	(+)	7	(-)	(-)	(-)
3	(+)	7	(-)	(+)	(+)
4	(+)	7	(-)	(+)	(-)
5	(+)	7	(+)	(+)	(+)
6	(+)	6	(+)	(+)	(-)
7	(+)	7	(+)	(+)	(-)
8	(+)	6	(+)	(+)	(-)

MPD; main pancreatic duct.

normal pancreas tends to be higher during arterial-phase than during pancreatic-phase imaging, and this result suggests that arterial-phase imaging combined with pancreatic-phase imaging may also be necessary to detect small or early pancreatic cancer. While contrast-enhanced CT is contraindicated in patients with symptoms of cardiac insufficiency, it is thought that differences in cardiac function between patients will affect the value of peak enhancement of the tumour, surrounding pancreatic tissue and AP-DT on the multiphasic study, so the scanning protocol needs to be adjusted in the case of a patient with reduced cardiac function.

Current MDCT technology has increased the speed of scanning, permitting routine use of very thin collimation with greater volume coverage. The volumetric data allow the creation of three-dimensional images or 2D reformations with higher spatial resolution. Quicker acquisition of data is possible during multiphase imaging with IV contrast administration, and greater arterial, pancreatic and portal venous enhancement can be achieved [2–4]. Bronstein et al [4] reported that sensitivity and accuracy in the diagnosis of pancreatic cancer have been improved significantly by the use of thin-section MDCT techniques. In that study, 18 patients with small pancreatic head cancer measuring 2 cm or smaller at pathological examination were included; in 14 of the 18 patients, a biliary stent had been inserted into the common bile duct, and the number of patients with pancreatic cancer at an early stage was not reported [4].

Although the sensitivity and accuracy in diagnosis of small pancreatic cancer has been improved significantly, it is still difficult to diagnose pancreatic cancer at an early stage. The difficulties in diagnosis of early pancreatic cancer on MDCT are thought to be due to the small

tumour size (<2 cm), loss of biliary dilatation, vascular involvement and mass effect, and little attenuation difference compared with normal pancreatic parenchyma. It has been reported that some pancreatic carcinomas show little attenuation difference compared with the normal pancreas during pancreatic-phase imaging, and may appear as iso- or high-attenuating tumours. Hijioka et al [15] reported a small pancreatic carcinoma with marked tumour enhancement during pancreatic parenchymal-phase and delayed-phase imaging, where fibrous tissue in the tumour was sparse, and where there was an increase in the number of dilated veins, in particular at the tumour margin. In the present study, the tumours appeared as high- to iso-attenuating on pancreatic and delayed-phase imaging in four cases, with the tumour size ranging from 8 mm to 12 mm (Figures 1 and 2).

Although in the present study the density of vascular structure in the tumours was not evaluated on histological examination, high- to iso-attenuating enhancement on pancreatic and delayed-phase imaging may be considered to reflect an abundant vascular structure in the smaller pancreatic tumours. Prokesch et al [16] reported that 6 of the 53 patients (11%) with pancreatic adenocarcinomas had iso-attenuating tumours, and reported that the interrupted duct sign may be the single most important sign of virtually iso-attenuating pancreatic adenocarcinoma because a dilated pancreatic duct was observed in all cases of virtually iso-attenuating tumours. Dilatation of the MPD can be depicted by axial CT images, but it is impossible to demonstrate the entire course of the MPD showing both stenosis and dilatation on a single axial CT image [16]. Curved reformation images can delineate both the pancreatic duct and the lesion causing the dilation of the pancreatic duct, making it easier to assess the relationship between

Table 3. Attenuation differences between normal pancreatic parenchyma and tumour (AD–PT) on multiphasic imaging (HU)

Case	NE	AP	PP	DP
1	10	15	–9	–19
2	0	7	–22	–24
3	9	9	–8	–9
4	9	10	–14	–56
5	7	30	20	–9
6	6	49	30	4
7	5	38	30	10
8	0	21	25	3
Mean	5.7 ± 4.0	22.8 ± 15.3	6.5 ± 21.8	–13.0 ± 21.1

NE, non-enhanced image; AP, arterial phase; PP, pancreatic parenchymal phase; DP, delayed phase.

Figure 5. AD-PT on multiphasic imaging. AD-PT=attenuation of pancreatic parenchyma – attenuation of tumour (HU).

the pancreatic duct and the lesion on one display [17, 18]. Four cases in the current study presented high- or iso-attenuating to normal pancreatic parenchyma on pancreatic and delayed-phase imaging, and two cases with tumours measuring 10 mm or less did not show associated pancreatitis or loss of normal lobar texture at the site of the lesion. In these cases, focal stenosis of the MPD with dilatation of the distal MPD on curved reformation images was useful for detecting lesions (Figures 1 and 2).

Shimizu et al [14] reported that dilatation of the MPD and associated pancreatitis were useful findings in the diagnosis of small pancreatic carcinoma. In their study, three cases of small pancreatic cancer with pancreatitis and accompanying MPD obstruction were reported. The associated pancreatitis showed a contrasting effect (black and white sign) between the areas of the pancreatic parenchyma proximal and distal to the site of the MPD obstruction [14]. The loss of normal lobar texture is caused by tumour spread destroying normal pancreatic parenchyma and is often observed on thin-section contrast-enhanced CT in patients with pancreatic cancer [4]. In this study, the patients with tumours measuring 10 mm or less did not show associated pancreatitis or loss of normal lobar texture. Although findings of associated pancreatitis and loss of normal lobar texture

are indications of pancreatic cancer, they are not always observed in cases of smaller tumours (Figures 3 and 4).

Only one patient had an abnormal elevation of tumour markers, with elevated serum CA19-9. Although CA19-9 is thought to be the most reliable serum marker for the diagnosis of pancreatic cancer, levels of CA19-9 are frequently normal in the early stages [19].

In our study, tumour sizes on CT images were not measured because the margins of tumours less than 2 cm tend to be unclear according to the phase of contrast study, but tumour sizes on pathological examination were evaluated for the purpose of analysis.

Although dilatation of MPD was observed in all cases, it is known that a small pancreatic cancer without dilatation of the main pancreatic duct is possible. Other pancreatic diseases, such as chronic pancreatitis, may present similar findings to early pancreatic cancer. The relationship between tumour differentiation and CT findings of early pancreatic cancer is not explained in our study. As the data in the current study were obtained from a small sample, we recognize the need for further studies involving a larger number of cases to resolve the issues concerning the diagnosis of early pancreatic cancer. However, the current study indicates that MDCT using contrast-enhanced multiphasic imaging and post-processed pancreatic duct images are useful

Figure 6. Relationship between tumour size and AD-PT during the pancreatic phase. There was a statistical difference between low-attenuated lesions and high-attenuated lesions in respect to the tumour size ($p < 0.01$), and there was a positive relationship between the tumour size and AD-PT ($r = 0.84$)

AD-PT, attenuation differences between normal pancreatic parenchyma and tumour; PP, pancreatic phase.

for detecting pancreatic cancer at an early stage, and patients suspected of having any pancreatic disease or dilatation of MPD need to be examined by MDCT to rule out pancreatic cancer.

Early pancreatic carcinomas tend to appear as low attenuation during early phase rather than during pancreatic phase, and appear as high- to iso-attenuation during the pancreatic and delayed phases in respect to the tumour size. Focal stenosis or obstruction of the MPD with dilatation of distal MPD on curved reformation imaging seem important in the diagnosis of early pancreatic cancer. Associated pancreatitis and loss of normal lobar texture may be also important, although absent in smaller tumours of less than 1 cm.

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