

# Imaging Finding Analysis and Prognosis Comparison of Pancreatic Head Cancer Invading the Peripheral Nerve Plexus Among Different Groups

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## Research Article

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# Abstract

**Background:** To compare imaging features and analyze prognostic differences among different groups with pancreatic head cancer invading the peripheral nerve plexus.

**Methods:** We reviewed preoperative multislice spiral CT (MSCT) images, complete surgical records, and postoperative pathological results of 93 patients with pancreatic head cancer and peripheral nerve invasion. Two radiologists who were unaware of surgical and pathological results evaluated the MSCT images to determine peripheral nerve invasion of pancreatic head cancer. A pathologist who was unaware of the imaging findings grouped the patients based on surgical records and pathological findings. Pancreatic head cancer invasion of the anterior neural pathway was assigned to group A and invasion of pancreatic plexus 1, pancreatic plexus 2, and root of the mesenteric pathway to group B. Both groups were evaluated for peripheral nerve invasion, tumor size, dilatation of the common bile duct/main pancreatic duct, duodenal invasion, and prognosis of pancreatic head cancer.

**Results:** A mass- and strand-like pattern or coarse reticular pattern was frequently observed when two groups of pancreatic head cancer invaded the peripheral nerve plexus. Intergroup differences in tumor size and common bile duct/main pancreatic duct dilatation were insignificant. The duodenal invasion rate was higher in group A than in group B; however, the intergroup difference was insignificant. The prognosis was poorer for group A than for group B.

**Conclusions:** Although the intergroup differences in radiographic findings were not significant, the prognosis was poorer for group A than for group B.

## Background

Patients with pancreatic cancer have an extremely poor prognosis, with the 5-year survival rate in these patients being approximately 6% [1]. Currently, surgery is the only way to improve the overall survival of these patients. However, even for patients who underwent surgery, the median survival is only 17 months [2]. Farrow et al. and Mitsunaga et al. reported that the most important factor resulting in poor postoperative prognosis was extrapancreatic perineural invasion (EPNI) caused by the characteristics of neurotrophic growth of pancreatic cancer, leading to postoperative recurrence [3, 4]. Chang et al. reported that the prognosis of patients with pancreatic head cancer and EPNI/duodenal invasion was significantly poorer [5].

Pathologically, the peripheral nerve plexus around the head of the pancreas is divided into four pathways (Fig. 1a). Pancreatic plexus 1 (PLX1) arises from the right celiac ganglion (CG) and passes behind the portal vein to the uncinate process of the pancreas (a typical neuroinvasive pathway for pancreatic head cancer). Pancreatic plexus 2 (PLX2) arises from the mesenteric ganglion (MG) near the superior mesenteric artery and extends along the posterior inferior pancreaticoduodenal artery (PIPDA)/jejunal trunk (JT) to the hook process. This is the most common invasive route for pancreatic uncinate process cancer. The root of the mesenteric pathway (ROM) involves PIPDA as in the case of PLX2. However, the

tumor does not extend toward the MG but grows along the tail of the nerve fibers toward the small intestinal mesentery. This is the second most common invasion route for pancreatic uncinata process cancer. The anterior neural pathway (AN) extends along the gastroduodenal artery (GDA), common hepatic artery (CHA), and hepatoduodenal ligament to the right CG. The PLX1, PLX2, and ROM pathways extend along the dorsal side of the pancreas and have an intersection point, the uncinata process of the pancreas. The AN is in the ventral side of the pancreas and does not pass through the uncinata process of the pancreas.

There is a consensus that the prognosis of pancreatic head cancer with EPNI is significantly poor [6–8]. However, we previously found that the imaging findings and prognosis of all patients with pancreatic head cancer and EPNI differ slightly. Therefore, in this study, we aimed to elucidate the imaging features and prognosis of patients with pancreatic head cancer involving the peripheral nerve plexus by dividing them into two groups according to the anatomical characteristics of the neural pathway: group A, patients showing pancreatic head cancer invasion of AN; and group B, patients showing invasion of PLX1, PLX2, or ROM.

## Methods

The preoperative MSCT images, surgical records, and pathological findings of pancreatic cancer patients who underwent Whipple surgery in our institution from December 2014 to December 2019 were reviewed. The study was approved by the institution's ethical review committee. The inclusion criteria were as follows:

- (1) Patients for whom enhanced MSCT scans were performed preoperatively in our institution and in whom the tumor was diagnosed to be a resectable pancreatic head tumor (Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines). According to our previous research [9], the CT diagnostic criteria for arterial and venous (superior mesenteric artery/vein, portal vein, celiac artery, and common hepatic artery) invasion should be dealt with slightly differently.
- (2) Whipple surgery in our institution and tumor was pathologically confirmed as pancreatic cancer with EPNI (Fig. 1b).

On the other hand, the following patients were excluded:

- (1) Patient with other major diseases that may affect the prognosis, such as other cancers and kidney failure;
- (2) patients who died of other sudden factors such as a cerebral infarction or a car accident;
- (3) patients (n = 6) whose MSCT scans showed simultaneous invasion noted in groups A and B owing to the large size or the special growth site of the mass. Accordingly, 93 patients were screened, of whom 43 were included in group A and 50 in group B. The mean age of the patients in groups A and B was 67.3 years (range 36–84 years) and 65.5 years (range 38–81 years), respectively.

# MSCT

Before CT, the gastrointestinal tract was filled with 500 ml of an aqueous solution. Images were obtained using a 256-row CT system (Revolution CT, GE Healthcare). A contrast agent was injected intravenously at a rate of 4 ml/s, and the total amount injected was 100 ml. Enhanced biphasic scanning consisting of breath-holding, arterial (35 s after injection) and intravenous (60 s after injection) phase scans with thicknesses of 0.63 mm was performed.

MSCT image interpretation, surgical review, and pathological outcome assessment

The images were evaluated by two abdominal radiologists who were unaware of the surgical or pathological results of the patients to assess the morphological features of the tumor and determine radiological evidence of peripancreatic nerve invasion. Differences in interpretation between the two radiologists were resolved through negotiations. A pathologist who was unaware of the MSCT findings carefully reviewed the complete surgical records of all patients, in particular the intraoperative judgment pertaining to the relationship between the tumor and the signature vessels of the neural pathway (e.g., the gastroduodenal artery [GDA], posterior inferior pancreaticoduodenal artery [PIPDA], and portal vein [PV]). The reviewer focused on the presence of pancreatic head cancer and grouping of peripheral nerve invasion in combination with postoperative pathological findings and surgical records.

## Patient follow-up

Overall survival was defined as the time from the first diagnosis of a pancreatic head tumor in our institution to the time of death. The date of death was obtained by the authors by follow-up over telephone.

## Statistical analysis

Univariate log-rank test was used for statistical evaluation. The imaging findings of pancreatic head cancer were evaluated using the chi-square test and independent sample T test, and the prognosis of pancreatic head cancer in the two groups was evaluated by performing the Kaplan-Meier survival analysis. A P-value of  $<.05$  was considered significant. All statistical analyses were performed using SPSS 25.0 software.

## Results

In our study, surgical exploration and postoperative pathological assessments confirmed that all cases were resectable without obvious invasion of the main peripancreatic vessels. The accuracy, sensitivity and specificity of MSCT for diagnosing EPNI were 92%, 92.5% and 85.7%, respectively.

The radiographic manifestations of pancreatic head cancer involving the peripheral nerve usually show a mass-and-strand pattern (a mass with diameter greater than 2-mm diameter mass or strand-shaped soft

tissue density connecting to the pancreatic head cancer) or a coarse reticular pattern (composed of thick reticular lines with less intermingled fat density) [10]. There was no evidence of any difference in the patterns of invasion of the peripheral nerve between groups A and B (Figure 2). In group B, the tumors invading the plexus often developed along more than one pathway, as shown in Figure 2b, whereby the tumors invaded both PLX2 and ROM as the nerve plexus was crisscrossing and complex. Furthermore, the pancreatic uncinata process cancer is more prone to multi-pathway invasion (PLX1, PLX2, and ROM) due to the close anatomical location, which was the important reason for their integration into group B.

## Tumor size

The two groups showed no significant difference in the size of pancreatic head carcinoma ( $P = 0.882$ ). The mean size of pancreatic head carcinoma in group A was  $3.0 \pm 0.94$  cm, while that in group B was  $3.0 \pm 0.92$  cm (Table 1).

## Common bile duct and main pancreatic duct dilatation

The two groups also showed no significant difference in the proportions of cases showing dilatation of the common bile duct and main pancreatic duct. The number of patients showing common bile duct dilatation in groups A and B was 24/43 (55.8%) and 29/50 (58%) respectively ( $P = 0.832$ ). The number of patients showing main pancreatic duct dilatation in groups A and B was 33/43 (76.7%) and 37/50 (74%), respectively ( $P = 0.76$ ) (Table 1).

## Duodenal invasion

Normal enhancement of the duodenal wall was interrupted, with uniform/nodular thickening of the duodenal wall, when the low-density pancreatic head tumor spread from the pancreas to the adjacent duodenal wall. Although the duodenal invasion in group A (26/43, 60.47%) showed an increasing trend in comparison with that in group B (24/50, 48%), the difference was not statistically significant ( $P = 0.229$ ). (Table 1)

Table 1  
Comparison and summary of general imaging findings of pancreatic head cancer between the two groups

Imaging demonstrated	Position classification		$\chi^2$	P
	A = 43	B = 50		
Tumor size	3.0±0.94	3.0±0.92	/	0.882
Common bile duct dilation	24 (55.81%)	29 (58.00%)	0.045	0.832
Main pancreatic duct dilation	33 (76.74%)	37 (74.00%)	0.094	0.76
Duodenal invasion	26 (60.47%)	24 (48.00%)	1.445	0.229

## Prognosis

The prognosis was significantly poorer when pancreatic head cancer involved AN (group A) in comparison with PLX1/PLX2/ROM (group B) (P = 0.001). The median survival time was 304 days in group A and 528 days in group B. (Figure 3)

## Discussion

Pancreatic cancer is one of the most aggressive human tumors. Complete surgical resection is the only known curable way for pancreatic cancer, but even patients who have undergone successful surgery often die of the disease due to metastases or relapses, which can be partly attributed to nerve invasion. Peripheral nerve invasion can be attributed to different mechanisms, and to date, three theories have been proposed to explain this finding. (i) Jin et al. identified lymphatic vessels in the superior mesenteric artery peripheral nerve plexus by immunohistochemical staining, providing factual evidence for the theory that tumor cell infiltration in neurogenic PNI was transmitted through lymphatic channels [11]. (ii) The "low resistance theory" proposed in the 1930s identified three weak points in the fascialis—the nerve endings, the blood vessels entering the nerve, and the reticular fibers entering the nerve—and suggested that cancer cells could easily invade and grow along the interfascialis space [12]. (iii) In 1994, Dale Bockman et al. observed high expression levels of transforming growth factor  $\alpha$  (TGF- $\alpha$ ) in nerve cells and high expression levels of epidermal growth factor receptor (EGFR) in cancer cells by electron microscopy, indicating the possibility of interactions between tumor cells and nerves [13]. Subsequently, numerous basic experiments gradually led to the theory of the neural microenvironment. This theory proposed that cells stimulated by cancer cells in the microenvironment could influence the occurrence of PNI-related processes through autocrine or paracrine mechanisms [14–16]. For example, pancreatic cancer releases colony-stimulating factor (CSF-1) to recruit macrophages, and cancer cells stimulate macrophages to secrete glial cell-derived neurotrophic factor (GDNF) to enhance the invasive ability of cancerous cells [20].

Pancreatic cancer with nerve invasion has been reported to significantly reduce progression-free survival and overall survival. Recent imaging studies focusing on preoperative determination of nerve invasion in pancreatic head cancer have confirmed the accuracy of MSCT in the diagnosis of EPNI and its effect on prognosis [18–22]. However, even in pancreatic head cancer with nerve invasion, individual patients show distinct differences in prognoses. Therefore, the present study attempted to further investigate the invasion of different pathways of the nerve plexus by pancreatic head cancer.

Although the surgical methods for Whipple surgery have continued to improve over decades of development, screening patients who are eligible for resection is more important to ensure greater patient benefits in the long run. Some scholars have proposed that surgical treatment is not recommended for patients who have been preoperatively diagnosed with EPNI/duodenal invasion of pancreatic cancer. However, since the peripheral nerve plexus invasion rate of pancreatic cancer can be as high as 53%-100% [23, 24], categorization of all patients with peripheral nerve invasion as unresectable may deprive some patients of the opportunity to undergo essential surgery. Therefore, we tried to group pancreatic head cancers involving different nerve plexuses on the basis of the findings of preoperative MSCT examinations, and preliminarily investigated the differences in prognosis among these groups to provide a theoretical basis for the subsequent exploration of treatment options for different groups.

From the embryological point of view, the pancreas originates from the ventral and dorsal pancreatic primordia, and a single pancreas is formed through the development and fusion of both primordia. The ventral pancreatic primordium forms the dorsal part of the head of the pancreas and the uncinete process of the pancreas, while the dorsal pancreatic primordium gradually develops into the ventral part of the head of the pancreas as well as the neck, body, and tail of the pancreas. The boundary between the ventral and dorsal pancreas, i.e., the line connecting the portal/superior mesenteric vein and the anterior edge of the intrapancreatic bile duct, can be roughly defined on CT images (Fig. 4). The ventral pancreas lies on the dorsal side of this boundary, while the dorsal pancreas occupies the ventral region [25, 26]. Pancreatic head cancer originating from the dorsal pancreas often invades the anterior nerve pathway. In contrast, pancreatic head cancer originating from the ventral pancreas often shows cancer cells invading PLX1, PLX2, and ROM. In addition, since the three pathways of nerve plexuses cross at the uncinete process of the pancreas and are located close to each other, pancreatic head cancers are prone to multi-pathway invasion of these nerve plexuses. On the basis of the differences in the anatomical locations of the four pathways of nerve plexus and the growth locations of pancreatic head cancer, this study divided pancreatic head cancers invading different pathways of the nerve plexus into two groups: pancreatic head cancers that invaded AN (group A), and those that invaded PLX1, PLX2, and ROM (group B).

Wang et al [27] found that the clinicopathological features of pancreatic head cancer arising from dorsal or ventral pancreas were different. The frequencies of some regional lymph node metastasis were different too. Tumors arising from dorsal pancreas were more likely to invade the common bile duct and duodenum than the others. Finally, their findings indicated that the pancreatic head cancer arising from ventral pancreas had a better survival outcome, which is consistent with our results. The weakness of their study [27] is that it is often difficult to accurately classify the primary tumor location on preoperative

CT imaging, and some patients could not be grouped. Differently, we speculate that it is feasible to divide the pancreatic head cancer into anterior and posterior groups according to the preoperative CT diagnosis of nerve invasion. Our study preliminarily confirmed the difference in prognosis between the two groups: group A, pancreatic head cancer anteriorly invading AN, showed worse prognosis than group B, pancreatic head cancer posteriorly invading PLX1/ PLX2/ROM.

The limitations of this study need to be acknowledged. First, this was a retrospective study, and the prognosis of patients with pancreatic head cancer with nerve plexus invasion in different groups still needs to be confirmed by further prospective studies. Second, the small sample size precluded adequate stratified studies. Third, traditional observation indicators such as lymph node invasion and surgical margin were not included in the evaluation criteria, because these indicators need to be confirmed by postoperative pathology and cannot be accurately diagnosed by preoperative CT. Fourthly, multivariate analysis of factors affecting postoperative survival of pancreatic head cancer was not conducted in this study, because EPNI is an independent prognostic factor affecting postoperative survival time of pancreatic head cancer[7].

## Conclusions

In summary, our study showed radiographic findings other than those pertaining to nerve invasion were not significantly different between pancreatic head cancer invading AN (group A) and PLX1/ PLX2/ROM (group B), but the prognosis of group A was evidently worse than that of group B. The clinical significance of preoperative MSCT diagnosis of pancreatic cancer groups A/B in the selection of treatment methods will be prospectively studied in the follow-up.

## Abbreviations

EPNI Extrapancreatic perineural invasion

AN Anterior neural pathway

PLX1 Pancreatic plexus 1

PLX2 Pancreatic plexus 2

ROM Root of the mesenteric pathway

GDA Gastroduodenal artery

PV Portal vein

PIPDA Posterior inferior pancreaticoduodenal artery

JT Jejunal venous trunk

CG Celiac ganglia  
MG Mesenteric ganglion  
SMA Superior mesenteric artery  
CHA Common hepatic artery  
PD Pancreatic duct  
IVC Inferior vena cava  
TGF- $\alpha$  Transforming growth factor  $\alpha$   
EGFR Epidermal growth factor receptor  
CSF Colony-stimulating factor  
GDNF Glial cell-derived neurotrophic factor

## Declarations

- **Ethics approval and consent to participate**

The ethics Committee of Shanghai Sixth People's Hospital approved the retrospectively registered study and waived the requirement for informed consent.

- **Consent for publication**

Not Applicable.

- **Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests.

- **Funding**

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## • Authors' contributions

H.L. and H.K.P., conceived the study. H.K.P., G.T., J.Q.Y. and N.H.Y. collected and provided patients' data and performed MR imaging annotation. L.P.Y. reviewed pathological sections. H.K.P. performed the statistical analysis. H.K.P., H.L. and N.H.Y. wrote and edited the manuscript. All authors reviewed and approved the final manuscript.

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## • Statement

All methods were carried out in accordance with relevant guidelines and regulations.

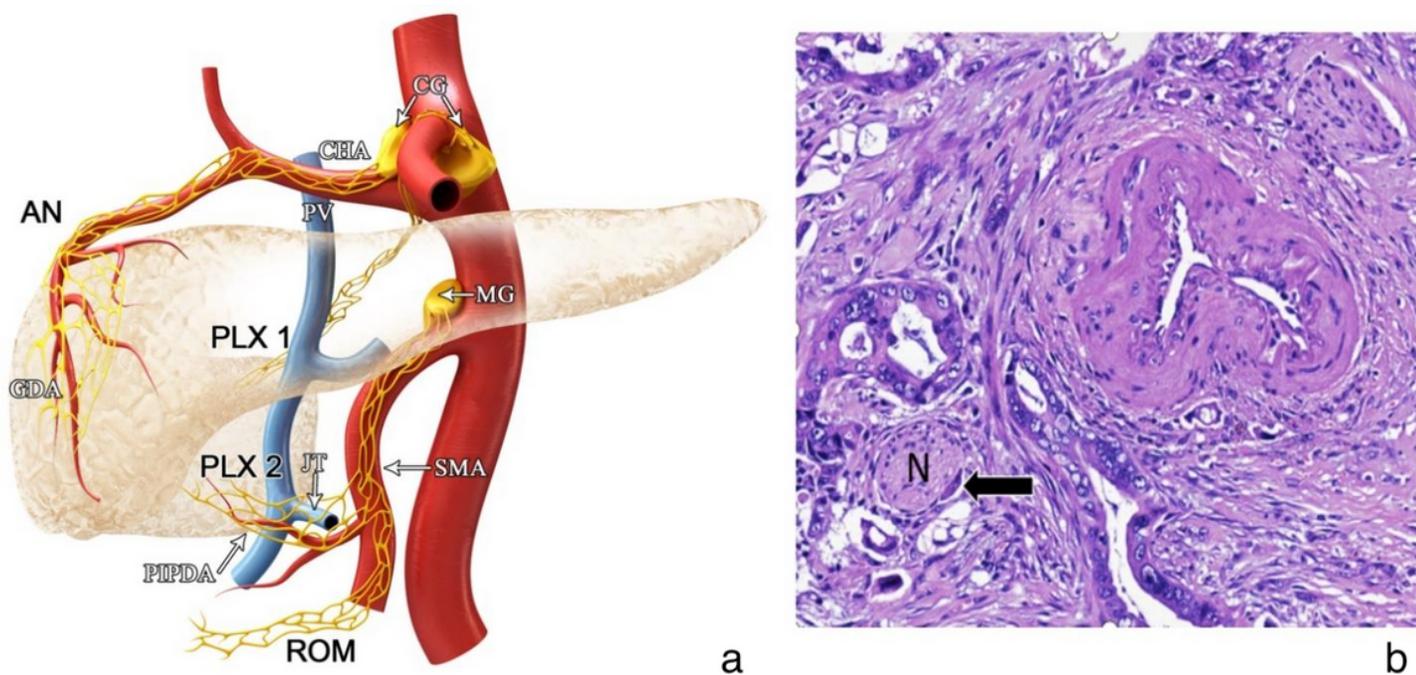
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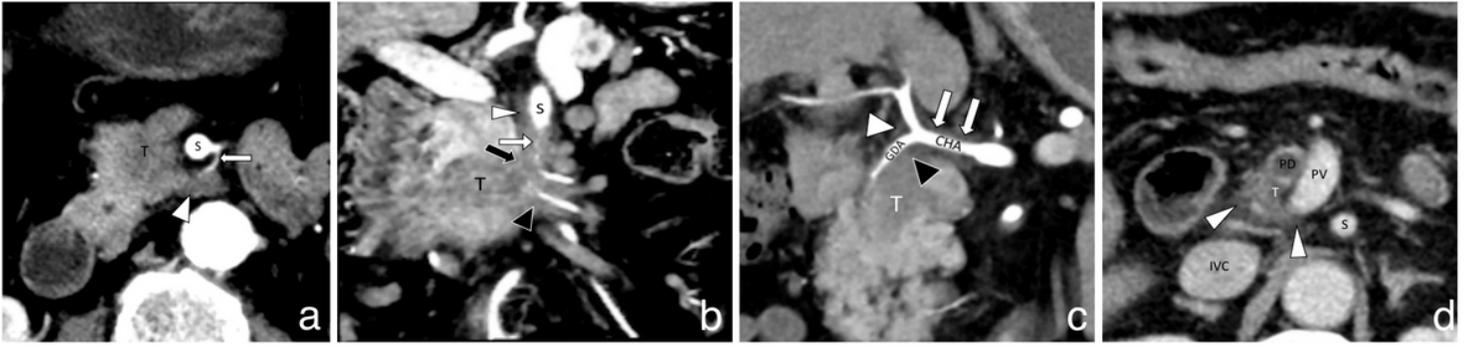
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## Figures



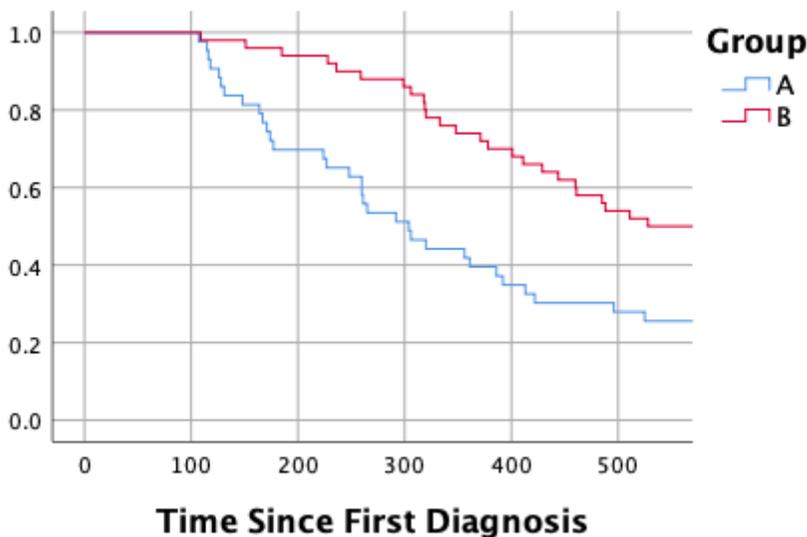
**Figure 1**

a: Anatomical diagram of nerve pathways around the head of the pancreas. AN = Anterior neural pathway; PLX1 = pancreatic plexus 1; PLX2 = pancreatic plexus 2; ROM = root of the mesenteric pathway; GDA = gastroduodenal artery; PV = portal vein; PIPDA = posterior inferior pancreaticoduodenal artery; JT = jejunal venous trunk; CG = celiac ganglia; MG = mesenteric ganglion; SMA = superior mesenteric artery; CHA = common hepatic artery. 1b: Pathological evidence of pancreatic cancer involving the peripheral nerves. Nerve bundles (N) infiltrated by cancer cells (arrow).



**Figure 2**

The radiographic manifestations of pancreatic head cancer involving the peripheral nerve plexus. 2a. Axial multislice spiral CT image. Pancreatic head cancer (T) infiltrating the inferior pancreaticoduodenal artery (arrow) along pancreatic plexus 2. Mass-and-strand pattern (arrowhead). S, superior mesenteric artery. 2b. Small field of view volume rendered constructed in 20° right coronal oblique and axial planes perpendicular to the plane of the superior mesenteric artery. Pancreatic head cancer (T) involves both pancreatic plexus 2 and the root of the mesenteric pathway. The mass completely surrounds (white arrow) the posterior inferior pancreaticoduodenal artery and infiltrates (white arrowhead) upward along the superior mesenteric artery (S). The mass also grows toward the root of the mesenteric pathway (black arrowhead). Mass and strand pattern (black arrow). 2c. Small field of view constructed the same as that in figure 2b. Pancreatic head cancer (T) infiltrates the gastroduodenal artery (GDA) along the anterior nerve plexus and extends to the common hepatic artery (CHA) (white arrow). Coarse reticular pattern (white arrowhead) and mass and strand pattern (black arrowhead). 2d. Axial multislice spiral CT image. Pancreatic head cancer extends along pancreatic plexus 1. A small tumor of the head of the pancreas (T) extends posteriorly to the portal vein (PV) in a coarse reticulation pattern (arrowhead). PD, pancreatic duct; IVC, Inferior vena cava; S, superior mesenteric artery.



### Figure 3

The Kaplan–Meier survival curve showed that the prognosis was significantly poorer when pancreatic head cancer involved the anterior nerve pathway (group A) in comparison with the invading pancreatic plexus 1/ pancreatic plexus 2/root of the mesenteric pathway (group B) ( $P = 0.001$ ).



### Figure 4

Schematic diagram of the rough demarcation line of the dorsal and ventral pancreas. Dotted lines connect the common bile duct (arrowhead) and the anterior margin of the superior mesenteric vein (arrow). The dorsal pancreas is located at the front of the dotted line, while the ventral pancreas is located at the back of the line.