

# Radical nerve dissection for the carcinoma of head of pancreas: report of 30 cases

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## Abstract

**Objective:** To explore the clinical value of the radical nerve dissection (RND) for the carcinoma of head of pancreas (CHP).

**Methods:** The clinical and pathological data of 30 CHP patients who underwent RND in our hospital were retrospectively analyzed, with an attempt to explore the safety and short-term efficacy of this procedure.

**Results:** Among these 30 patients, the operative time was (351±61) min, the intra-operative blood loss was 350 (range, 300–600) mL, and the grades B and C pancreatic fistula was 23.33%. During the follow-up (range, 2–30 months; median: 17 months), the 1-year survival rate was 63.33% and the 1-year disease-free survival rate was 56.67%. Among the 23 patients (76.66%) with positive extra-pancreatic perineural invasion (PNI), the 1-year case-fatality rate was 34.78%, which was not significantly different from that (28.57%) of patients with negative PNI (P=0.760).

**Conclusions:** Our results suggested potential advantages of RND in the fields of surgery-associated risk and prognosis compared with the Whipple operation in the treatment of CHP. Due to the low sample size of this study, further well-designed research of large sample size is needed.

**Keywords:** Pancreatic cancer; pancreatic ductal adenocarcinoma; radical nerve dissection (RND); perineural invasion (PNI); pancreaticoduodenectomy

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## Introduction

With an increasing prevalence, the pancreatic cancer has an extremely poor prognosis, with an overall 5-year survival rate being only 1–6% (1–3). Currently surgery is the only way for the radical treatment of pancreatic cancer (4). In 1940s, the Whipple procedure (pancreatoduodenectomy) was introduced for the treatment of carcinoma of head of pancreas (CHP). However, it has only a low resection rate (10–20%) (5,6). Even in pancreatic cancer patients who had achieved the radical resection, the post-operative 5-year survival rate still was as low as 10–20%. Perineural invasion (PNI) has been found to be a key cause of local relapse and poor prognosis in pancreatic cancer patients after the operation. Peri-pancreatic nerve dissection might play a role in the radical treatment of

pancreatic cancer (7). Therefore, the radical nerve dissection (RND) for the CHP was introduced in our department in 2012, with an attempt to improve the prognosis of patients with pancreatic cancer. This article retrospectively analyzes the clinical and pathological data of 30 patients who had undergone this procedure in our department, with an attempt to explore the safety and short-term efficacy of RND.

## Materials and methods

### General data

The clinical and pathological data of 30 patients with pathologically confirmed pancreatic cancer who had undergone RND in our department from June 2012 to June

2014 were retrospectively analyzed.

### *Pre-operative assessment and management*

The ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI) were routinely performed. The serum tumor markers including CA19-9, CEA, and CA12-5 were measured. Preoperative bile drainage was performed in patients with a serum total bilirubin (TB) level of  $\geq 220$   $\mu\text{mol/L}$ . Multidisciplinary consultations were organized for patients with unknown etiologies.

### *Surgical maneuvers*

The nerve tissues at the retroperitoneum around the pancreas were dissected, which included: (I) nerves and soft tissues between the inferior vena cava (including the aortic plexus) and the abdominal aorta were removed; (II) after the skeletonization of the hepatoduodenal ligament, the nerves and soft tissues (including the whole lymph node station 12) in this ligament was dissected; (III) the common hepatic artery was isolated and then its surrounding nerves and soft tissues (including lymph node station 8) were dissected; (IV) the celiac trunk was isolated and then its surrounding nerves and soft tissues (including lymph node station 9) were dissected; (V) the root of the mesenteric artery was dissected to open the vascular sheath, and then the membranous fold at the uncinate process was removed along its right side, followed by the dissection of the nerves and soft tissues at the right half (including lymph node station 14); and (VI) the nerves and soft tissues (including lymph node station 16a2 and 16b2) in the dense post-pancreatic connective tissue that fix the pancreas at the abdominal trunk-aorta-superior mesenteric artery axis were also dissected. With an attempt to achieve radical resection, both the portal vein and the superior mesenteric vein might be removed in patients with portal vein involvement.

### *Postoperative adjuvant therapy*

Gemcitabine monotherapy (1,000  $\text{mg/m}^2$  D1 and D8; 21 days per cycle, for six cycles) was applied in all patients. While no specific treatment protocol was assigned for local recurrence and distant metastasis with or without local recurrence, the treatment protocol must meet the *NCCN Clinical Practice Guidelines in Oncology* (2012-2015 editions).

### *Follow-up*

Patients were followed up every 1 month during the

first post-operative half year, and then every 3, 6 months later. During the follow-up visits, the routine blood tests, biochemistry, determination of gastrointestinal tumor markers, and ultrasound were performed. An enhanced CT scan was performed every 3 months to identify any possible tumor relapse.

### *Pathological assessment of PNI*

PNI is regarded as positive if pathology shows that the tumor cells have covered the nerve surface, infiltrated the epineurium, or entered the nerve tract, or if the tumor cells have infiltrated any layer of the 3-layer nerve sheath, or if the tumor cells have covered one third of the peripheral structures of nerves. Based on the findings under the light microscopy (100 $\times$ ), the PNI was divided into four grades: no infiltration (0 involved nerve); mild infiltration (1-5 involved nerves); moderate infiltration (6-10 involved nerves); and severe infiltration (over 10 involved nerves). The extra-pancreatic nerve plexuses were grouped according to the Japan Pancreatic Society grouping criteria [1986]: (I) pancreatic head plexus (Plx ph), this plexus can be further divided into two parts, one being the direct route from the right celiac ganglia to the upper internal side of the uncinate process [the first part of pancreatic head plexus (Plx ph1)] and the other route extending from the superior mesenteric artery (SMA) to the upper internal side of the uncinate process [the second part of pancreatic head plexus (Plx ph2)]; (II) abdominal cavity plexus (Plx ca); (III) plexus around the SMA (Plx sma); (IV) plexus in the hepatoduodenal ligament (Plx hdl); (V) aortic plexus (Plx aor); and (VI) splenic plexus (Plx sp). Nerve infiltration confirmed by pathology indicates the presence of the plexus involvement, which represents a positive nerve invasion.

### *Statistical analysis*

Statistical analyses were performed using SPSS Statistics 16.0 (IBM Chicago, IL, USA). The Fisher's exact test for non-parametric variables, was considered statistically significant since two-sided value of P is smaller than 0.05.

## **Results**

### *General data*

The clinical and pathological data of 30 patients with pathologically confirmed pancreatic cancer who had undergone RND in our department from June 2012 to

June 2014 were retrospectively analyzed. Among these 30 patients, there were 17 men and 13 women aged ( $59.80 \pm 10.21$ ) years, with a body mass index (BMI) of ( $22.12 \pm 2.01$ ).

### Clinical and pathological parameters

According to the UICC/AJCC staging criteria (7<sup>th</sup> edition) [2010], 2 patients (6.67%) were in stage I<sub>A</sub>, 4 (13.33%) in stage I<sub>B</sub>, 3 (10.00%) in stage II<sub>A</sub>, and 21 (70.00%) in stage II<sub>B</sub>. Pancreatic ductal adenocarcinoma was confirmed in all these 72 patients, and the disease was well differentiated in 8 cases (26.67%), moderately differentiated in 13 cases (43.33%), and poorly differentiated in 9 cases (30%). The rate of positive surgical margin was 13.3%, and the number of the positive lymph nodes ranged 11 to 56 (median: 26) (Table 1).

### Pathological features of the involved intra- and extra-pancreatic nerves

PNI is regarded as positive if pathology shows that the pancreatic tumor cells have infiltrated the perineural gaps or penetrated the epineurium and entered the nerve tract. The

intra-pancreatic nerve infiltration level was scored according to the method described by Zhu *et al.*, among which the score was 0 in 8 cases (26.67%), 1 in 6 cases (20.00%), 2 in 6 cases (20.00%), and 3 in 10 cases (33.33%). The extra-pancreatic nerve plexus was divided into six groups according to the *Guidelines on the Management of Pancreatic Cancer* published by Japan Pancreatic Society in 1986. Serial sections showed that the Plx ph had the highest involvement rate, among which the positive rate was 66.67% for Plx ph1 and 70.00% for Plx ph2. Furthermore, the positive rate was 56.67%, 56.67%, 30.00%, 40.00%, and 10.00% for Plx ca, Plx sma, Plx hdl, Plx aor, and Plx sp.

### Intra-operative conditions

The operative time was ( $351 \pm 61$ ) min and the intra-operative blood loss was ( $418 \pm 265$ ) mL. Of these 32 patients, 12 (40.00%) required blood transfusion and 8 (26.67%) required the resection and reconstruction of superior mesenteric vein (Table 2).

### Complications

Diagnosis and grading of pancreatic fistula were based on the diagnostic criteria established by the International Study Group on Pancreatic Fistula (ISGPF). Fourteen patients (46.67%) developed pancreatic fistula after the surgery, among whom 7 (23.33%) were in grade A, 7 (23.33%) in grade B, and none (0%) in grade C. Other complications included bile leak (n=1, 3.33%), delayed gastric emptying (n=8, 26.67%), abdominal abscess (n=3, 10%), and incision infection (n=3, 10%). No perioperative death was noted. The average hospital stay was ( $15.6 \pm 3.1$ ) days. One patient (3.33%) suffered from intractable diarrhea after the post-operative neoadjuvant chemotherapy (gemcitabine monotherapy), which was resolved after treatment with somatostatin (Table 3).

### Survival

During the follow-up (range, 2-30 months; median: 17 months) till January 2015, the 1-year survival rate was 63.33% and the 1-year disease-free survival rate was 56.67%.

### Correlation between nerve invasion and prognosis

Among the patients with positive intra-pancreatic PNI, the 1-year mortality was 31.81%, which was not significantly different from that (37.50%) of patients with negative PNI (P=0.548). Till the analysis deadline, the case-fatality rate was the same (50%) in patients with positive and negative

**Table 1** Clinical and pathological features of 30 patients

Clinical features	Cases (n, %)
T stage	
T1	2, 6.67
T2	9, 30.00
T3	19, 63.33
N stage	
N0	9, 30.00
N1	21, 70.00
UICC stage	
IA	2, 6.67
IB	4, 13.33
IIA	3, 10.00
IIB	21, 70.00
Differentiation	
Poorly differentiated	9, 30.00
Moderately differentiated	13, 43.33
Well differentiated	8, 26.67
Cutting margin	
Positive	4, 13.33
Negative	26, 86.67
Number of positive lymph nodes	26 (range, 11-56)

**Table 2** Intra-operative conditions in 30 patients

Items	Results
Operative time (min, mean $\pm$ SD)	351 $\pm$ 61
Intra-operative blood loss (mL, mean $\pm$ SD)	418 $\pm$ 265
Percentage of patients requiring blood transfusion (n, %)	12, 40.00
Percentage of patients requiring vein resection (n, %)	8, 26.67

SD, standard deviation.

**Table 3** Post-operative complications in 30 patients

Complications	Cases
Pancreatic fistula (ISGPF) (n, %)	
A	7, 23.33
B	7, 23.33
C	0, 0
Bile leak (n, %)	1, 3.33
Delayed gastric emptying (n, %)	8, 26.67
Abdominal abscess (n, %)	3, 10
Incision infection (n, %)	3, 10
Intractable diarrhea (n, %)	1, 3.33
Hospital stay (day, mean $\pm$ SD)	15.6 $\pm$ 3.1
Perioperative death (n, %)	0, 0

ISGPF, International Study Group on Pancreatic Fistula; SD, standard deviation.

intra-pancreatic PNI. Among the patients with positive extra-pancreatic PNI, the 1-year mortality was 34.78%, which was also not significantly different from that (28.57%) of patients with negative PNI [ $P=0.571$  (Table 4)]. Survival analysis also showed that there was no significant differences in the field of prognosis between patients with PNI or those without PNI (Figure 1).

## Discussion

Due to the neurotropic growth pattern of the pancreatic cancer, patients with this disease often have a low incidence of PNI. In addition, the residual tumor cells inside the nerve tissues are key causes of tumor relapse (7). RND, that radical treatment of pancreatic cancer in combination with peripancreatic nerve dissection, had been reported in a few domestic and foreign countries, showing good clinical efficacy; thus, this strategy has a high value in improving the long-term survival of patients (8). In a Japanese center, the standard Whipple operation plus extensive lymph node

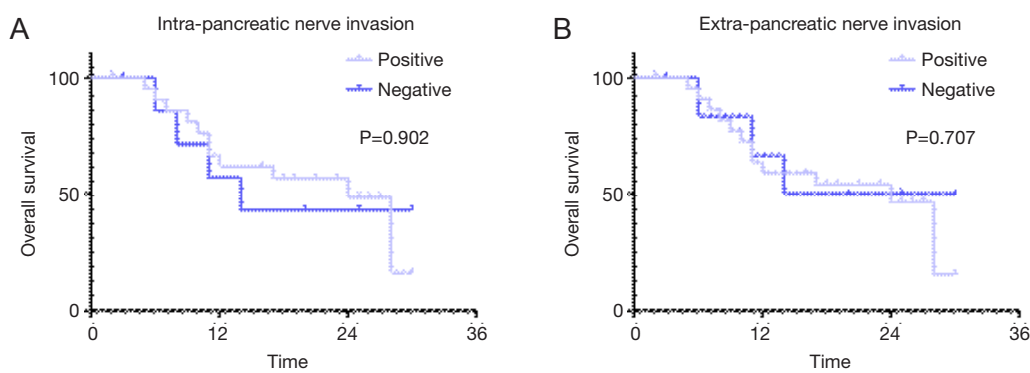
dissection (including the dissection of lymph node station 16) following the resection of retroperitoneal connective tissues dramatically improved the survival (9). According to Matsuno *et al.*, while the resection rate of pancreatic cancer had reached 40% in Japan, patients with relatively long survival were only seen among patients who had also received the peripancreatic nerve resection; meanwhile, lymph node dissection, even together with the resection of large blood vessels, had limited effectiveness in improving the long-term survival rate of pancreatic cancer patients (8). Therefore, RND including dissection of the involved nerves is useful for removing the latent tumor cells and thus further improves the surgical effectiveness of pancreatic cancer. However, few clinical trials have explored the role of RND; multicenter prospective randomized controlled studies with larger sample sizes should be performed to further clarify the dissection extent, identify the indications, evaluate the surgical safety, and thus further confirm its clinical value in improving the prognosis.

In the Guidelines on the *Management of Pancreatic Cancer* published by the Japan Pancreatic Society in 2003, the peripancreatic nerve plexuses were divided into six groups: (I) pancreatic head plexus: this plexus can be further divided into two parts, one being the direct route from the right celiac ganglia to the upper internal side of the uncinate process and the other route extending from the superior mesenteric artery (SMA) to the upper internal side of the uncinate process; (II) abdominal cavity plexus; (III) SMA plexus; (IV) plexus in the hepatoduodenal ligament; (V) aortic plexus; and (VI) splenic plexus. The first five plexuses have a close relation with the pancreatic head cancer. In our current study, based on the distribution of the pancreatic head plexus and the possible tumor involvement, we performed radical pancreaticoduodenectomy in patients with pancreatic head cancer, followed by the dissection of peri-pancreatic nerves including groups 1, 2, 4, and 5 nerve plexuses and part of group 3 plexus (the latter mainly included the right side of the SMA). Meanwhile, we have conducted a multicenter prospective randomized controlled study to assess the safety of RND and to evaluate whether long-term efficacy of this operation procedure was superior to the traditional Whipple operation. Our current analysis on 30 enrolled cases showed that this procedure was basically comparable to the standard Whipple operation in terms of complications, intra-operative blood loss, average length of hospital stay, and perioperative case-fatality rate, suggesting that the RND did not increase the surgical risks. However, due to the short follow-up period, we only

**Table 4** Analysis of the possible correlation between nerve invasion and prognosis in 30 patients

Pathology of perineural invasion	Case (n)	Death within 1 post-operative year (n, %)	P value*	Death till the deadline (n, %)	P value*
Intra-pancreatic nerve invasion					
Positive	22	7, 31.81	0.770	11, 50.00	1.000
Negative	8	3, 37.50		4, 50.00	
Extra-pancreatic nerve invasion					
Positive	23	8, 34.78	0.760	12, 52.17	0.666
Negative	7	2, 28.57		3, 42.86	

\*, Fisher's exact test.



**Figure 1** Overall survival analysis of (A) intra-pancreatic nerve invasion and (B) extra-pancreatic nerve invasion.

evaluated the short-term survival. The 1-year survival was 63.33% among patients who had undergone this procedure, which was slightly higher than that (55.95%) in 2,340 pancreatic cancer patients in an epidemiological survey, suggesting that RND has a potential role in improving the prognosis (10).

Pancreatic cancer patients with positive extra-pancreatic nerve plexus infiltration often have remarkably lower survival rate than those with a negative finding (7,11). It has been reported that the average 1-, 2-, and 3-year survival rates were 30%, 6%, and 0%, respectively in pancreatic cancer patients with nerve metastasis but could be as high as 52%, 32%, and 18%, respectively, in those without nerve metastasis. The differences were statistically significant (12). Even in patients with a small pancreatic cancer (less than 2 cm in diameter), the 5-year survival ranged 15%-40% if peri-pancreatic nerve PNI occurred, and most patients died of local relapse and/or distant metastasis (13,14). As shown in our current study, the survivals were similar between PNI-positive patients and PNI-negative patients, suggesting there was no significant correlation between

PNI condition and prognosis in patient who had undergone this procedure. Therefore, the standardized RND can be clinically meaningful for resolving the high relapse caused by PNI.

However, although the peri-pancreatic nerves may be invaded by the pancreatic cancer, these nerve plexuses should not be casually resected because they have key roles in regulating the gastrointestinal functions. Authors from Kanazawa Medical School had already found that the metabolic and nutritional management after extended radical operation for pancreaticobiliary carcinoma could be extremely challenging because the patients suffered from uncontrollable diarrhea (known intractable diarrhea) (15). It had been proposed that the intractable diarrhea might be caused by the complete dissection of the nerve plexus around the SMA. Therefore, in our practices we only dissected the nerve plexus 180° at the right side of the SMA; notably, only one patient experienced the intractable diarrhea in our series. However, dissection of the right side of the SMA only may not be able to achieve R0 resection and the complete removal of the uncinate process of

pancreas. Therefore, the exact extent of the dissection of tissues (in particular the nerves) around the SMA warrants further investigations.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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