Risk factors related to metastasis of para-aortic lymph nodes in pancreatic ductal adenocarcinoma

A retrospective observational study

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Abstract
This study was designed to explore the risk factors related to metastasis of para-aortic lymph node (PALN).

Clinicopathologic data of 241 patients with resectable or borderline resectable pancreatic cancer who underwent pancreaticoduodenectomy with extended lymphadenectomy between January 2008 and December 2015 were collected, potential factors related to metastasis of PALN were analyzed.

Positive rate of PALN was 19.5% (47/241). Univariate analysis showed that back pain ($P<.001$), CA19-9 preoperative level ($P<.001$), tumor size ($P<.001$), portal vein (PV)/superior mesenteric vein (SMV) invasion ($P<.001$), superior mesenteric artery (SMA) invasion ($P<.001$), and diameter > 1.0 cm were in correlation with PALN involvement, multivariate analysis revealed that preoperative CA19-9 level, PV/SMV invasion, SMA invasion and diameter > 1.0 cm were independent risk factors to metastasis of PALN. Patients with LN8+ had a higher positive rate of PALN than with LN8− (38.1% vs 15.6%, $P=.001$), similar results could be found when LN12+ (35.8% vs 13.2%, $P<.001$) and LN14+ (41.2% vs 11.0%, $P<.001$), multivariate analysis showed that LN8+ and LN14+ were closely in correlation with PALN metastasis.

Several factors were related to the status of PALN, preoperative CA19-9 level, PV/SMV invasion, SMA invasion and diameter > 1.0 cm were 4 independent risk factors to PALN metastasis. LN8+ and LN14+ were 2 strong predictors of PALN metastasis. A comprehensive analysis covering all possible risk factors related to metastasis of PALN should be given before design of treatment plan whenever involvement of PALN was suspected.

Abbreviations: ISGPS = International Study Group for Pancreatic Surgery, LN = lymph node, OS = overall survival, PALN = para-aortic lymph node, PV = portal vein, SMA = superior mesenteric artery, SMV = superior mesenteric vein.

Keywords: metastasis, pancreatic cancer, para-aortic lymph node, risk factor

1. Introduction
Pancreatic cancer characterized by low resection rate and poor prognosis has become one of the leading causes of cancer-related death. As an example, median survival time of patients with PALN metastasis ranged from 5.1 to 15.7 months reported by some centers. Involvement of PALN was the single independent factor associated with a shorter survival time confirmed by a study designed by Doi et al., and the similar results could be found in some other studies designed by Murakami et al., Sakai et al., Yoshida et al., Kanda et al., and so on.

It is important and necessary to predict the status of PALN before operation and to analyze factors related to metastasis due to its pivotal role for prognosis of patients with pancreatic cancer, the status of PALN is one of the critical factors for designing the therapeutic regimen. As the nonregional lymph nodes, metastasis of PALN is deemed as a contraindication of surgery by some authors although contrary opinions are held by others. A certain proportion of patients may lose the opportunity of surgery on account of the suspected metastasis of PALN when pancreatic cancer is diagnosed. Negative PALN may be found for some of these patients if pathological examination is carried out because of the false-positive results of imaging. It has important significance to evaluate the status of PALN accurately whenever pancreatic cancer is confirmed. Most frequently, CT and MRI are used to judge the status of lymph node before operation, or to evaluate the resectability of pancreatic cancer. However, imaging-based preoperative detection techniques have yielded disappointing results, the accuracy of CT or MRI is 72.5% or 88.4% for detecting PALN metastasis. As mentioned above, PALN has been classified as nonregional lymph node, and
metastasis of PALN has been recognized as distant metastasis. Because of the very poor prognosis when PALN involved, surgical resection is not considered for pancreatic cancer. This may be the pivotal limiting factor. Judgment of PALN status is mainly relied on imaging examination for patients without operation, consequently, accuracy of PALN status is unavoidably weakened. Risk factors related to metastasis of PALN should be analyzed carefully, which may help to improve judgment accuracy and to make better treatment plan. With the aim of exploring risk factors, extended lymphadenectomy with No. 16a2 and No. 16b1 lymph nodes included has been performing for pancreatic head cancer in our hospital recent years.

2. Materials and methods

2.1. Patients enrolled in this study

Clinicopathological data of patients with ductal adenocarcinoma of pancreatic head confirmed by pathological examination postoperatively who underwent standard or extended pancreaticoduodenectomy with extended lymphadenectomy between January 2008 and December 2015 were collected and analyzed. Inclusion criteria: resectable or borderline resectable pancreatic head cancer based on the definition of NCCN Guidelines 2018; pancreatic ductal adenocarcinoma was confirmed by postoperative pathology. Exclusion criteria: carcinomas of lower end of common bile duct, ampulla, duodenal papilla, and uncinate process; neuroendocrine neoplasm; acinar cell carcinomas; benign tumors; patients who underwent neoadjuvant therapy. The protocol and procedures employed were reviewed and approved by the institutional review committee of Beijing Chaoyang Hospital.

2.2. Definitions

PALNs were dissected from the level of the celiac trunk down to the root of the inferior mesenteric artery, including stations No.16 a2 and No.16 b1. In this study, standard or extended pancreaticoduodenectomy was consistent with the definitions recommended by International Study Group for Pancreatic Surgery (ISGPS). Lymph nodes of stations 5, 6, 8a, 8p, 9, 12a, 12p, 12b1, 12b2, 12c, 13a-b, 14a-d, 16a2, 16b1, and 17a-b were removed, which was defined as extended lymphadenectomy.

2.3. Evaluation before operation

Either contrast-enhanced CT or MRI was used for evaluation of resectability and judgment of lymph node status, especially the status of nonregional lymph node including PALN. Metastasis of lymph node was suspected when the greatest diameter was >1.0 cm.

2.4. Adjuvant therapy after operation

Patients with ECOG 0-1 were suggested to receive adjuvant therapy within 8 to 12 weeks after operation. Regimes including gemcitabine, gemcitabine plus capecitabine, capecitabine, and FOLFIRINOX (leucovorin and fluorouracil plus irinotecan and oxaliplatin) were selected. Radiotherapy was recommended for patients with positive margin.

2.5. Factors for analysis

The following potential risk factors for PALN metastasis were analyzed: general factors included age at diagnosis, gender, back pain or not, preoperative CA19-9 level; imaging factor mainly included the diameter of PALN observed in computed tomography; pathologic factors covered tumor size, tumor differentiation, portal or superior mesenteric vein (PV/SMV) invasion, superior mesenteric arterial (SMA) invasion. Meanwhile, we also analyzed the station of lymph node (LN) which was in close relationship with the status of PALN.

3. Results

3.1. General parameters

A total of 241 patients including 108 males and 133 females with ductal adenocarcinoma of pancreatic head were enrolled in this study. The age of patients at diagnosis ranged from 40 to 79 years, with a median age of 57 years. The CA19-9 level before operation ranged from 17 to 1848 U/mL, with a median of 156 U/mL. Twenty-five patients suffered from back pain preoperatively. Tumor size ranged from 1.4 to 6.4 cm, with a median of 2.5 cm. As classification of the 8th edition AJCC/UICC TNM staging system, T1 was found in 43 patients, T2 in 169 patients and T3 in 29 patients, respectively. PV/SMV invasion was found in 47 patients, SMA invasion was found in 24 patients. Swollen PALN (diameter >1.0 cm) observed in CT scan was found in 44 patients. Among these patients, 213 patients received chemotherapy: gemcitabine for 46 cases, gemcitabine + capecitabine for 83 cases, capecitabine for 55 patients, and FOLFIRINOX for 29 patients. Of the 213 patients, 21 patients received radiation therapy: gemcitabine for 46 cases, gemcitabine + capecitabine for 83 cases, capecitabine for 55 patients, and FOLFIRINOX for 29 patients. A total of 5431 lymph nodes were detected, and the number of lymph nodes retrieved ranged from 6 to 45 with a median number of 21 per patient. Five hundred eighty-one PALNs were retrieved (ranged from 1 to 5 with a median of 2). Lymph node involvement was detected in 164 patients (68.0%), number of patients at different station of lymph node is shown in Fig. 1, and PALN metastasis was confirmed in 47 patients (19.5%). As classification of the 8th edition AJCC/UICC TNM staging system, N0 was found in 77 patients, N1 in 52 patients and N2 in 112 patients. The greatest diameter of positive PALN ranged from 0.5 to 1.6 cm with the median diameter of 1.1 cm, and 0.3 to 1.2 cm with the median diameter of 0.6 cm was examined in patients with negative PALN.

3.2. Lymph nodes

Univariate analysis showed that age at surgery, gender, and BMI were not the risk factors to metastasis of PALN. Patients with back pain had a higher positive rate of PALN metastasis compared to patients without ($P = .028$); preoperative CA19-9
level was another potential risk factor, a significantly higher positive rate of PALN metastasis was found when CA19-9 was more than 1000 U/mL ($P < .001$). Several pathologic factors including tumor size, PV/SMV invasion, and SMA invasion were in correlation with metastasis of PALN. As classification of the 8th edition AJCC/UICC TNM staging system, tumor size ≤2 cm, >2 and ≤4 cm, >4 cm was defined as T1, T2, and T3, respectively. Patients were divided into 3 groups according to the current classification, different positive rates of PALN were revealed. Patients had the highest positive rate of 58.6% when tumor size was >4 cm compared to 7.0% when ≤2 cm. Patients with PV/SMV invasion or SMA invasion had the higher positive rate than without, diameter > 1 cm was also correlated to high metastasis rate of PALN, as shown in Table 1. Multivariate analysis showed that preoperative CA19-9 level, PV/SMV invasion, SMA invasion and diameter >1 cm were 4 independent risk factors to metastasis of PALN, which are listed in Table 2.

### 3.4. Relationship between different stations of LNs and metastasis of PALN

As univariate analysis shown in Table 3, much more patients with positive PALN when patients had metastasis of the 8th station of LN compared with nonmetastasis of LN8 (38.1% vs 13.6%, $P = .001$), similar results were found when metastasis was confirmed in LN12, LN13, and LN14. Whereas no significantly different proportion of patients with positive PALN was detected in LN5, LN6, LN9, and LN17, similar proportions of patients with PALN involvement were found regardless of the status of these stations. Multivariate analysis showed that LN8+ and LN14+ were 2 strong predictors to metastasis of PALN.

### 3.5. Different survival time of patients with or without PALN metastasis

As shown in Table 4, patients with PALN involvement had a much poorer prognosis compared to patients without. The 1-year overall survival rate (OS) was 79.4% in patients with negative PALN, but only 52.7% in patients with positive PALN. A 5-year OS of 22.6% was calculated in patients without PALN involvement, whereas no 3-year survival was found in patients with PALN involvement, let alone 5-year survival (Fig. 2).

### 4. Discussion

Among all malignant solid tumors, pancreatic cancer is characterized by delayed diagnosis, low curative rate, and high

| Factors                        | No. of patients | Positive rate of PALNs (%) | $P$   |
|--------------------------------|-----------------|----------------------------|-------|
| Age, y                         |                 |                            | .624  |
| ≤50                            | 95              | 21.1                       |       |
| >50                            | 146             | 18.5                       |       |
| Gender                         |                 |                            | .071  |
| Male                           | 108             | 25                         |       |
| Female                         | 133             | 15                         |       |
| BMI, kg/m²                     |                 |                            | .166  |
| <25                            | 185             | 22.2                       |       |
| ≥25, <30                       | 29              | 10.3                       |       |
| ≥30                            | 27              | 11.1                       |       |
| Back pain                      |                 |                            | .028  |
| Yes                            | 25              | 36.0                       |       |
| No                             | 216             | 17.6                       |       |
| Preoperative CA19-9 level, U/mL|                 |                            | <.001 |
| ≤500                           | 185             | 11.9                       |       |
| >500, ≤1000                    | 35              | 34.3                       |       |
| >1000                          | 21              | 61.9                       |       |
| Tumor size, cm                 |                 |                            | <.001 |
| ≤2                             | 43              | 7.0                        |       |
| >2, ≤4                         | 169             | 16.0                       |       |
| >4                             | 29              | 58.6                       |       |
| Tumor differentiation          |                 |                            | .258  |
| Poorly                         | 152             | 21.7                       |       |
| Well/moderately                | 89              | 15.7                       |       |
| PV/SMV invasion                |                 |                            | <.001 |
| Yes                            | 47              | 40.4                       |       |
| No                             | 194             | 14.4                       |       |
| SMA invasion                   |                 |                            | <.001 |
| Yes                            | 24              | 66.7                       |       |
| No                             | 217             | 14.3                       |       |
| Diameter of PALN > 1.0 cm      |                 |                            | <.001 |
| Yes                            | 41              | 88.6                       |       |
| No                             | 200             | 4.1                        |       |

| BMI = body mass index, PALN = para-aortic lymph node, PV = portal vein, SMA = superior mesenteric artery. |
mortality.

Cancer Statistics in China which is completed by National Cancer Center of China shows that the estimated new cancer cases and deaths of pancreas are 90.1 and 79.4 thousand in 2015. With the increasing incidence and also with the high mortality, pancreatic cancer has been becoming a major public problem. Despite decades of effort, pancreatic cancer remains one of the most aggressive and lethal malignancies, and its 5-year survival rate remains at only ~5%.

Poor prognosis is in correlation with several factors, a key factor confirmed by centers is metastasis of PALN. As the nonregional lymph nodes, metastasis of PALN has been recognized as distant metastasis, that is to say, a large proportion of patients with PALN involvement will lose the opportunity to receive operation. Before the design of treatment plan, estimation of clinical staging is an essential process. The status of PALN is one of focus of attention, and judgment is mainly based on CT or MRI. Metastasis is highly suspected when diameter of lymph node is more than 1.0 cm, and patient with diameter of PALN > 1.0 cm will lose the opportunity of operation. However, false positive of imaging is unavoidable, and several other factors may help us to improve the accuracy of judgment. Thus, it is necessary to explore the high-risk factors related to metastasis of PALN.

Recently, judging the status of PALN are mainly dependent on imaging examinations including abdominal CT, MRI, or PET-CT if operation is avoided. While, imaging-based preoperative detection techniques have yielded disappointing results. A study designed by Imai et al showed the 0 sensitivity of CT, MRI, and PET-CT for detecting PALN metastasis, and the accuracy was 72.5%, 88.4%, and 90.0%, respectively. Meanwhile, their study confirmed that no significant difference was found for longer diameter between metastatic and nonmetastatic PALN, same results could also be found for shorter diameter and long/short ratio although diameter of PALN > 1 cm was confirmed as an independent risk factor in this study. However, metastasis of PALN could not be ruled out when diameter was no more than 1.0 cm. If potential risk factors to metastasis of PALN can be confirmed, it may help to improve the accuracy of preoperative diagnosis. There are few of studies about high-risk factors related to metastasis of PALN. A study designed by Komo et al showed that PV/SMV invasion, tumor size > 3 cm and regional lymph node metastasis were associated with high involvement rate of PALN. Our study showed that back pain, high CA19-9 level (more than 500 U/mL, especially more than 1000 U/mL), larger than 4 cm of tumor size, PV/SMV invasion, and SMA invasion were independent risk factors to metastasis of PALN. Based on our results, patients who had extremely high CA19-9 level, or PV/SMV and/or SMA invasion detected on imaging examination at diagnosis should be highly suspected to have PALN metastasis although no swollen lymph nodes were found in the para-aortic area.

Which stations of LN should be involved when PALN metastasis happened? Several researches in this area have been concluded, as an example, using the technique of injecting activated carbon particles or 111In colloid, Nagakawa et al concluded that passing stations 13 and 14 were the main lymphatic route to PALN. Kayahara et al showed that the main lymphatic pathway from the head of pancreas to PALN was via the station 14, a study designed by Kanda et al found that LN12+, LN14+, and LN17+ were independent risk factors to metastasis of PALN, thus station 14 was deemed as “junctural LN” by some centers. In the present series, a higher positive rate of PALN was found when LN8, LN12, LN13, or LN14 was involved, and multivariate analysis showed that involvement of LN8 and LN14 were independent relative factors to metastasis of PALN. Owing to the close correlation between the 2 stations, we
want to know whether LN16 should be removed if metastasis of LN14 is highly suspected during operation procedure although extended lymphadenectomy is not recommended for pancreatic cancer.

Most of studies confirmed that patients with PALN involvement have decreased survival time.\cite{8,12,30,31} As an example, a study designed by Murakami et al\cite{12} showed that the 1-, 2-, 3-, and 5-year OS rates were 79%, 49%, 29%, and 23% in patients without metastasis of PALN, whereas 1-, 2-, and 3-year OS rates were 53%, 12%, and 0% in patients with metastasis of PALN. In this study, patients with PALN involvement had a poorer prognosis compared with patients without.

The main drawback of this study is the small sample which collected from our single center, meanwhile, several important influence factors have not been included in this study. With the aim to drawing a definitive conclusion, a big sample from multicenter which included more comprehensive risk factors is an urgent need.

In conclusions, patients with metastasis of PALN have poorer prognosis. Several factors are related to metastasis of PALN, besides the diameter > 1.0 cm, preoperative CA19-9 level, PV/SMV invasion, and SMA invasion are also 3 independent risk factors. Status of LN8 and LN14 are in correlation with PALN, a higher positive rate can be found when metastasis is confirmed in LN8 or LN14. A comprehensive analysis covering all possible risk factors related to metastasis of PALN should be given before design of treatment plan whenever involvement of PALN was suspected.

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**References**

[1] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[2] Ducrueux M, Cunha AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(suppl 5):v56–68.
[3] Paella S, Malleo G, Maggino L, et al. Pancreatectomy with para-aortic lymph node dissection for pancreatic head adenocarcinoma: pattern of nodal metastasis spread and analysis of prognostic factors. J Gastrointest Surg 2015;19:1610–20.
[4] Yamada S, Nakao A, Fuji T, et al. Pancreatic cancer with paraaortic lymph node metastasis: a contraindication for radical surgery? Pancreas 2009;38:e13–7.
[5] Sho M, Murakami Y, Motosi F, et al. Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients. J Gastroenterol 2015;50:694–702.
[6] Moon HJ, An JY, Heo JS, et al. Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. Pancreas 2006;32:37–43.
[7] Lin JY, Zhang XM, Kou JT, et al. Analysis of prognostic factors for pancreatic head cancer according to para-aortic lymph node. Cancer Med 2016;5:2701–7.
[8] Paulson AS, Cao HST, Tempero MA, et al. Therapeutic advances in pancreatic cancer. Gastroenterology 2013;144:1316–26.
[9] Shimada K, Sakamoto Y, Sano T, et al. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic
curative resection with extended lymphadenectomy for pancreatic carcinoma. J Am Coll Surg 2006;203:345–52.

[10] Sakai M, Nakao A, Kaneko T, et al. Para-aortic lymph node metastasis in carcinoma of the head of the pancreas. Surgery 2003;137:606–11.

[11] Doi R, Kami K, Ito D, et al. Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. World J Surg 2007;31:147–54.

[12] Murakami Y, Uemura K, Sudo T, et al. Prognostic impact of para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma. World J Surg 2010;34:1900–7.

[13] Kanda M, Fuji T, Naga S, et al. Pattern of lymph node metastasis spread in pancreatic cancer. Pancreas 2011;40:951–5.

[14] Yoshida T, Matsumoto T, Sasaki A, et al. Outcome of paraaortic node-positive pancreatic head and bile duct adenocarcinoma. Am J Surg 2004;187:736–40.

[15] Imai H, Doi R, Kanazawa H, et al. Preoperative assessment of para-aortic lymph node metastasis in patients with pancreatic cancer. Int J Clin Oncol 2010;15:294–300.

[16] Paiella S, Sandini M, Gianotti L, et al. The prognostic impact of para-aortic lymph node metastasis in pancreatic cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2016;42:616–24.

[17] Hartwig W, Vollmer CM, Fingerhut A, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). Surgery 2014;156:1–4.

[18] Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156:591–600.

[19] Zhang XM, Fan H, Kou JT, et al. Resection of portal and/or superior mesenteric vein and reconstruction by using allogeic vein for pT3 pancreatic cancer. J Gastroenterol Hepatol 2016;31:1498–503.

[20] Väsen H, Ibrahim I, Ponce CG, et al. Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European Expert Centers. J Clin Oncol 2016;34:2010–9.

[21] Baker H. Surveillance benefit for pancreatic cancer in high-risk individuals. Lancet Oncol 2016;17:e227.

[22] Wolfgang CL, Herman JM, Laberu DA, et al. Recent progress in pancreatic cancer. CA Cancer J Clin 2013;63:318–48.

[23] Wengen FA, Peter F, Zieren J, et al. Prognosis factors in carcinoma of the head of the pancreas. Dig Surg 2000;17:29–35.

[24] Parsons CM, Sutcliffe JL, Bold RJ. Preoperative evaluation of pancreatic adenocarcinoma. J Hepato-biliary Pancreat Surg 2008;15:429–35.

[25] Karmazanovsky G, Fedorov V, Kubyshkin V, et al. Pancreatic head cancer: accuracy of CT in determination of resectability. Abdom Imaging 2005;30:488–500.

[26] de Bondt RB, Nelemans PJ, Hofman PA, et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. Eur J Radiol 2007;64:266–72.

[27] Komo T, Murakami Y, Kondo N, et al. Prognostic impact of para-aortic lymph node micrometastasis in pancreatic ductal adenocarcinoma. Ann Surg Oncol 2016;23:2019–27.

[28] Nagakawa T, Kobayashi H, Ueno K, et al. Clinical study of lymphatic flow to the paraaortic lymph nodes in carcinoma of the head of the pancreas. Cancer 1994;73:1155–62.

[29] Kayahara M, Nagakawa T, Kobayashi H, et al. Lymphatic flow in carcinoma of the head of the pancreas. Cancer 1992;70:2061–6.

[30] Tammi EP, Balachandran A, Bhosale PR, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin North Am 2012;50:407–28.

[31] Aristu J, Canon R, Pardo F, et al. Surgical resection after preoperative chemoradiotherapy benefits selected patients with unresectable pancreatic cancer. Am J Clin Oncol 2003;26:30–6.