Retrospective Study

Risk factors for lymph node metastasis in patients with pancreatic neuroendocrine neoplasms

Yosuke Nakao, Hiromitsu Hayashi, Yo-ichi Yamashita, Ofuchi Takashi, Kazuki Matsumura, Norio Uemura, Fumimasa Kitamura, Rumi Itoyama, Toshihiko Yusa, Katsunobu Taki, Tatsunori Miyata, Takaaki Higashi, Shigeki Nakagawa, Hirohisa Okabe, Katsunori Imai, Hideo Baba

Specialty type: Gastroenterology and hepatology
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind

Abstract

BACKGROUND
Although PNENs generally have a better prognosis than pancreatic cancers, some PNENs display malignant behavior including lymph node (LN) metastasis. Complete tumor resection can be the only potentially curative treatment for patients with resectable PNENs. However, the indications for LN dissection are still controversial. Over the last decade, minimally invasive surgery such as laparoscopic pancreatic surgery (LPS) has been increasingly performed for pancreatic tumors including PNENs.

AIM
To investigate the risk factors for LN metastasis in PNENs and to select appropriate patients for limited surgery by LPS.

METHODS
From April 2001 to December 2019, 92 patients underwent pancreatic resection for PNENs at Kumamoto University Hospital. Finally, 82 patients were enrolled in this study. Using perioperative factors, we examined the predictive factors for LN metastasis in PNENs.

RESULTS
Among the 82 patients, the percentage of LN metastasis according to the pathological findings was 12% (10/82 cases). The median tumor size was 12 mm (range: 5-90 mm). The median tumor size in the LN-positive group (37 mm) was significantly larger than that in the LN-negative group (12 mm) (P = 0.0001). Multivariate analyses revealed that larger tumor size (≥ 20 mm) was an inde-
pended risk factor for LN metastasis (odds ratio 16.8, \( P = 0.0062 \)). In patients with small tumors (≤ 10 mm), LN metastasis was not found.

**CONCLUSION**

Larger tumor size (≥ 20 mm) is an independent risk factor for LN metastasis in PNENs. In smaller PNENs (≤ 10 mm), we may be able to choose limited surgery without LN dissection.

**Key Words:** Lymph node metastasis; Pancreatic neuroendocrine neoplasms; Risk factor; Tumor size

---

**INTRODUCTION**

Pancreatic neuroendocrine neoplasms (PNENs) are relatively rare and represent 1%-2% of all pancreatic neoplasms[1]. Although patients with PNENs generally have better prognosis than those with pancreatic cancers, some PNENs display malignant behavior including local invasion, lymph node (LN) metastasis, and distant metastasis[2]. The natural history of PNENs is not fully understood because of their relative rarity, and therefore, it is difficult to predict the malignant potential of PNENs precisely.

Complete tumor resection can be the only potentially curative treatment for patients with resectable PNENs. However, optimal surgical management procedures have not yet been established[3,4]. Especially, the indications for LN dissection are still controversial, especially in early PNENs. This is partly caused by the difficulty of predicting LN metastasis. Therefore, it is important to establish appropriate indications for LN dissection to treat PNENs.

Over the last decade, minimally invasive surgery such as laparoscopic pancreatic surgery (LPS) has been increasingly performed for pancreatic tumors including PNENs[5-7]. Non-comparative studies have shown that LPS for pancreatic tumors is safe and equivalently effective to open pancreatic surgery (OPS)[8-10]. In well-selected groups of patients with pancreatic lesions, LPS provides good peri and post operative outcomes, such as reduced intraoperative blood loss, and postoperative pain and length of postoperative day[8,10-13]. As a limited type of LPS, laparoscopic spleen-preserving distal pancreatectomy and excisional resection for PNENs has also been performed in selected cases[7,14,15]. However, the indications for limited surgery by LPS for patients with PNENs remain unclear.

The aims of this study are to investigate the risk factors for LN metastasis in PNENs and to select appropriate patients for limited LPS.

---

**MATERIALS AND METHODS**

**Study cohort**

From April 2001 to December 2019, 92 patients underwent pancreatic resection for PNENs at Kumamoto University Hospital. Of them, 10 patients (11%) were excluded from this analysis because of distant metastases and coexisting tumors other than PNENs. Finally, 82 patients were enrolled in this study. The patients were identified retrospectively from a prospectively maintained database, and additional data were obtained by reviewing each patient’s medical records. Written informed consent was obtained from all patients before treatment, and this study was approved by the Institutional Review Board of Kumamoto University (number 1291).
**Treatment strategy**

Before treatment, all patients underwent routine diagnostic laboratory tests and imaging modalities including enhanced computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS). The final diagnoses were confirmed pathologically using resected specimens. Tumors were classified as functional PNENs according to the clinical signs and symptoms of hormonal excess and increased levels of corresponding serum peptides and hormones. Tumors were classified as non-functional if they were not associated with distinct clinical manifestations or hormonal alterations[16]. Surgical procedures were selected based on each tumor’s location and extent and the patient’s general condition. Pancreatic resection was considered the first-choice treatment for patients with PNENs.

**Postoperative workup**

After treatment, all of the patients underwent regular follow-up examinations including routine laboratory tests and imaging studies including EUS, CT, or MRI to detect any pancreatic recurrence or distant metastasis, as described previously[17]. When tumor recurrence was confirmed, various treatment modalities were selected, including repeat surgery, chemotherapy, or a combination of these methods, according to tumor location and patient condition.

**Statistical analysis**

Continuous variables were expressed as median (range). Continuous and categorical variables were compared using Mann-Whitney U and χ² tests, respectively. Survival analyses were performed using the Kaplan-Meier method, with comparisons using the log rank test. Overall survival (OS) was calculated from the date of surgery until death or last follow-up. Variables in which the P value for LN metastasis was < 0.05 in univariate analysis were subjected to subsequent multivariate analysis by stepwise backward elimination procedures. All statistical analyses were performed using JMP® version 13.1 (SAS institute, Cary, NC, United States). All P values were two-sided, and P < 0.05 was considered as statistically significant.

**RESULTS**

The 82 patients’ demographic and clinical characteristics are summarized in Table 1. There were 41 male and 41 female patients, with a median age of 59 years (range, 18-81 years). Thirty five patients (43%) had symptoms at the first consultation. Preoperative contrast-enhanced CT showed that the majority of patients had tumors with hyper enhanced pattern (72 patients, 88%). Of the 31 patients (38%) who had functional PNENs, the most frequent type of functional PNEN was insulinoma (26 patients, 32%), followed by glucagonoma (2, 2.5%), gastrinoma (2, 2.5%), and VIPoma (1, 1%). There were 51 patients (62%) who had non-functional PNENs. Their 2017 WHO classifications were: G1, 70 (85%); G2, 9 (11%); and G3 or NEC, 3 (4%). Fourteen patients (17%) had multiple tumors, and the median tumor size was 12 mm (range, 5-90 mm). Among the 82 patients, 23 (28%) received pancreatoduodenectomy (PD), 38 (46%) received distal pancreatectomy, 2 (2.5%) received PD + DP, and 19 (23%) received enucleation or partial pancreatectomy.

Among the 82 patients, 10 (12%) were identified as having LN metastasis. The demographic and clinical characteristics of the 10 patients with LN metastasis were compared with those of the 72 patients without LN metastasis (Table 1). LN metastases of PNENs were positively associated with pathological grade: 6%, 44%, and 67% of cases with LN metastases were classified as G1, G2, and G3/NEC, respectively (P = 0.0009). In the LN metastasis-positive group, tumor size was significantly larger than that in the negative group (median, 12 vs 37, P = 0.0001). Univariate analysis showed that the following three factors were related to LN metastasis: tumor size ≥ 20 mm (Odds Ratio (OR) 31.5, P < 0.0001), WHO 2017 classification ≥ G2 (OR 20.1, P = 0.0001), and non-functional type of PNEN (OR 6.43, P = 0.035). Multivariate logistic regression analyses revealed that tumor size ≥ 20 mm was an independent risk factor for LN metastasis (OR 16.8, P = 0.0062) (Table 2).

Figure 1 shows the rate of LN metastasis according to tumor size. The rates of LN metastasis according to tumor size were as follows: 0% (0/29 cases, ≤ 10 mm group), 3% (1/31 cases, 11 mm-20 mm group), 25% (2/8 cases, 21-30 mm group), 50% (3/6 cases, 31-40 mm group), and 50% (4/8 cases, > 40 mm group) (Figure 1). The median length of follow-up after surgery was 51.8 months (range, 0.4-224.2). The cumulative OS rate after surgery for patients with no LN metastasis was significantly higher than that for those with LN metastasis (P = 0.009) (Figure 2).

**DISCUSSION**

PNENs are rare tumors[1]. The oncological history is not yet fully understood due to their often-lazy course, because it is not easy to find correct diagnosis and treatment. Furthermore, PNENs have wide variety biological behaviors, such as benign tumors and malignant status[18]. Because of the hetero-
Table 1 Comparisons of patients’ characteristics according to the presence of lymph node metastasis of pancreatic neuroendocrine neoplasm

| Variables                              | Total (n = 82) | N− (n = 72) | N+ (n = 10) | P value |
|----------------------------------------|----------------|-------------|-------------|---------|
| Age, median (range)                    | 59 (18-81)     | 58 (18-80)  | 63 (18-81)  | 0.65    |
| Gender (male/female)                   | 41/41          | 35/37       | 6/4         | 0.50    |
| Tumor size, median, mm (range)         | 12 (5-90)      | 12 (5-90)   | 37 (12-75)  | 0.0001  |
| Tumor number (single/multiple)         | 68/14          | 59/13       | 9/1         | 0.50    |
| Tumor location (Ph/Pb/Pt/Ph and Pt)    | 32/23/25/2     | 23/22/25/2  | 9/1/0/0     | 0.15    |
| Symptoms (yes/no)                      | 35/47          | 31/41       | 4/6         | 0.85    |
| CT Enhancement (hyper/hypo)            | 72/10          | 64/8        | 8/2         | 0.17    |
| Type of PNEN, n (%)                    |                |             |             | NS      |
| Insulinoma                             | 26 (32)        | 26          | 0           |         |
| Gastrinoma                             | 2 (2.5)        | 1           | 1           |         |
| Glucagonoma                            | 2 (2.5)        | 2           | 0           |         |
| VIPoma                                 | 1 (1)          | 1           | 0           |         |
| Non functional                         | 51 (62)        | 42          | 9           |         |
| WHO classification 2017, n (%)         |                |             |             | 0.0009  |
| NET G1                                 | 70 (85)        | 66          | 4 (6%)      |         |
| NET G2                                 | 9 (11)         | 5           | 4 (44%)     |         |
| NET G3/NEC                             | 3 (4)          | 1           | 2 (67%)     |         |
| Surgical procedure, n (%)              |                |             |             | NS      |
| Pancreatoduodenectomy (PD)             | 23 (28)        | 15          | 8           |         |
| Distal pancreatectomy (DP)             | 38 (46)        | 37          | 1           |         |
| PD + DP                                | 2 (2.5)        | 2           | 0           |         |
| Enucleation/partial pancreatectomy      | 19 (23)        | 18          | 1           |         |

N−: Negative for lymph node metastasis; N+: Positive for lymph node metastasis; NEN: Neuroendocrine neoplasms; WHO: World Health Organization; NET: Neuroendocrine tumor; PD: Pancreatoduodenectomy; DP: Distal pancreatectomy; CT: Computed tomography; PNEN: Pancreatic neuroendocrine neoplasm. NS: Not significant.

Nogeneity of PNENs, it is very difficult both to construct the effective clinical treatment policy systems and to confirm the surgical method for cure.

Some reports have associated LN metastasis with shorter OS[3,19-25], while others have found that LN status did not affect survival[26-29]. LN metastasis is positively correlated with pathological grade, with 15%-20%, 30%-40%, and > 50% of patients with LN metastasis classified as G1, G2, and G3, respectively[30]. In our study, we also reported that the LN metastasis-positive group of PNENs had poor OS after surgery. Further, we reported that LN metastases of PNENs are positively associated with pathological grade, with 6%, 44%, and 67% of patients with LN metastases classified as G1, G2, and G3/NEC, respectively (P = 0.0009; Table 1). Therefore, patients with PNENs and LN metastasis have poor prognosis and high malignant potential. However, previous reports have not clearly shown that to omit LN dissection may increase the possibility of recurrence. Some previous studies shows that local LN metastases of PNENs have oncologic effects[30,31]. A past study related with non-functional G1 PNENs who underwent surgery of pancreas reported that LN metastases of PNENs do not adversely affect oncological outcomes and do not require routine local lymphadenectomy[32]. Partelli et al[33] reported that a lot of insulinomas (well-differentiated) and non-functional PNENs located in the distal pancreas are very small, rarely associated with LN metastases, and there is no radiographic evidence of positive of LN metastases. Thus, the significance of LN metastasis in patients with PNENs is very complicated, and the indications for regional LN dissection are still controversial.

Previous studies have focused on the associations of LN metastasis or and/or prognosis with tumor size[17,21,34-39]. Although LN metastasis has been seen even in patients with tumors < 10 mm, LN metastasis occurs more often in patients with large tumors than in those with smaller ones. In our study, there were no cases of LN metastasis in patients with tumors ≤ 10 mm. LN metastases of PNENs were
Table 2 Factors related to lymph node metastasis of pancreatic neuroendocrine neoplasm

| Factors                        | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | Odds ratio          | P value               | Odds ratio | 95%CI    | P value |
| Age ≥ 60                       | 0.54                | 0.40                  |            |          |         |
| Gender (male)                  | 0.63                | 0.50                  |            |          |         |
| Symptoms (yes)                 | 1.13                | 0.85                  |            |          |         |
| CT Enhancement (hyper)         | 4                   | 0.17                  |            |          |         |
| Tumor number (multiple)        | 1.98                | 0.50                  |            |          |         |
| Tumor size (≥ 20 mm)           | 31.5                | <0.0001               | 16.8       | 2.15-35.4| 0.002   |
| WHO classification 2017 (≥ G2) | 20.1                | 0.0001                | NS         |          |         |
| Type of PNEN (non functional)  | 6.43                | 0.035                 | NS         |          |         |

NEN: Neuroendocrine neoplasms; WHO: World Health Organization; CT: Computed tomography; PNEN: Pancreatic neuroendocrine neoplasm; NS: Not significant.

Figure 1 Rate of lymph node metastasis according to tumor size. The rates of lymph node metastasis according to tumor size were as follows: 0% (0/29 cases, ≤ 10 mm group), 3% (1/31 cases, 11 mm-20 mm group), 25% (2/8 cases, 21-30 mm group), 50% (3/6 cases, 31-40 mm group), and 50% (4/8 cases, > 40 mm group). LN: Lymph node.

positively associated with tumor size, being present in 0%, 3%, 25%, and 50% of patients with primary tumors ≤ 10 mm, 11-20 mm, 21-30 mm, and > 30 mm, respectively. If we can predict the presence of LN metastasis according to tumor size, we can select appropriate patients for limited LPS.

Over the last decade, the use of laparoscopy in pancreatic surgery has increased significantly, and previously almost all open surgery can now be performed in a minimally invasive method. In general, these minimally invasive surgery should be limited to high-volume centers with extensive experience in pancreatic surgery with open surgery. Patients with small-sized PNENs in the body and tail of the pancreas are particularly well suited for minimally invasive surgery, and the laparoscopic procedures gives better result than open surgical method[40,41]. Laparoscopic distal pancreatectomy have the potential to be superior to the open surgical method in patients with benign tumors, resulting in less operative bleeding, shorter postoperative days, and equivalent rates of complications[13]. According to the review by 11 studies, which involve 906 PNENs patients, of whom 22% and 78% underwent LPS and OPS, respectively, it reported that overall complication rate of laparoscopic method was significantly lower (38% vs 46%, P < 0.001) and the postoperative days in hospital is shorter (P < 0.001) [40]. LPS is now considered to be a safe approach for PNENs and should be included in the patient’s surgical equipment. Many surgeons have reported that the rates of overall complication in small or benign tumors were lower with LPS than OPS. Although in the cases of patients with malignant PNENs, we need advanced surgical skills, LPS was not associated with compromised oncologic resection and provided benefits including reduced postoperative pain, shorter hospital stay, and shorter postoperative recovery period. Thus, it is important to investigate the risk factors of LN metastases in PNENs and to select appropriate patients for limited LPS. Our results offer certain recommendations in this regard.
Figure 2 Overall survival after surgery of 82 patients according to the presence of lymph node metastasis. The cumulative overall survival rate after surgery among patients who had no lymph node (LN) metastasis was significantly higher than that for those who had LN metastasis. LN: Lymph node.

However, this study had several limitations, including its retrospective design, the small number of subjects, and the lack of data on certain pathologic variables (especially the Ki-67 indices and mitotic rates) for all patients. The number of examined LNs was not sufficient, and data on the number of positive LNs were not available for all PNENs. Therefore, further research regarding advanced PNENs is required.

CONCLUSION
In conclusion, larger tumor size (≥ 20 mm) is an independent risk factor for LN metastasis in PNENs. In smaller PNENs (≤ 10 mm), we may be able to choose limited surgery without LN dissection.

ARTICLE HIGHLIGHTS
Research background
The indications for lymph node (LN) dissection are still controversial.

Research motivation
Over the last decade, minimally invasive surgery such as laparoscopic pancreatic surgery (LPS) has been increasingly performed for pancreatic tumors including pancreatic neuroendocrine neoplasms (PNENs).

Research objectives
The aim of this study was to investigate the risk factors for LN metastasis in PNENs and to select appropriate patients for limited surgery by LPS.

Research methods
From April 2001 to December 2019, 92 patients underwent pancreatic resection for PNENs at Kumamoto University Hospital. Finally, 82 patients were enrolled in this study. Using perioperative factors, we examined the predictive factors for LN metastasis in PNENs.

Research results
Among the 82 patients, the percentage of LN metastasis according to the pathological findings was 12% (10/82 cases). The median tumor size was 12 mm (range: 5-90 mm). The median tumor size in the LN-positive group (37 mm) was significantly larger than that in the LN-negative group (12 mm) \((P = 0.0001)\). Multivariate analyses revealed that large tumor size (≥ 20 mm) was an independent risk factor for LN metastasis (odds ratio 16.8, \(P = 0.0062\)). In patients with small tumors (≤ 10 mm), LN metastasis
was not found.

**Research conclusions**

Large tumor size (≥ 20 mm) is an independent risk factor for LN metastasis in PNENs. In smaller PNENs (≤ 10 mm), we may be able to choose limited surgery without LN dissection.

**Research perspectives**

In smaller PNENs (≤ 10 mm), we may be able to choose limited surgery without LN dissection.

**FOOTNOTES**

**Author contributions:** Nakao Y, Hayashi H and Yamashita Y designed the research study; Nakao Y, Takashi O, Matsumura K, Uemura N, Kitamura F, Itoyama R, Yusa T, Taki K, Miyata T, Higashi T, Nakagawa S, Okabe H and Imai K performed the research; Yamashita Y and Baba H contributed new reagents and analytic tools; Nakao Y, Hayashi H and Takashi O analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

**Institutional review board statement:** Institutional Review Board of Kumamoto University (number 1291).

**Informed consent statement:** Consent was obtained from the patient and family according to Institutional Review Board protocols.

**Conflict-of-interest statement:** All the authors have no conflicts of interest in association with this study. No financial support was received for the work described in this manuscript.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** Japan

**ORCID number:** Yosuke Nakao 0000-0002-6156-1421; Hiromitsu Hayashi 0000-0002-1832-4287; Yo-ichi Yamashita 0000-0001-8439-6666; Oftuchi Takashi 0000-0001-6219-5278; Kazuki Matsumura 0000-0002-6204-9147; Norio Uemura 0000-0003-3192-4153; Fumimasa Kitamura 0000-0002-6717-3788; Rumi Itoyama 0000-0003-1785-7599; Toshihiko Yusa 0000-0002-0970-8262; Katsunobu Taki 0000-0001-6532-5947; Tatsunori Miyata 0000-0003-4749-4741; Takaaki Higashi 0000-0002-1034-8671; Shigeki Nakagawa 0000-0003-3994-4028; Hirohisa Okabe 0000-0003-3041-7563; Katsunori Imai 0000-0003-0549-1825; Hideo Baba 0000-0002-6982-3457.

S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Liu JH

**REFERENCES**

1. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; 26: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

2. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; 19: 1727-1733 [PMID: 18515795 DOI: 10.1093/annonc/mdn351]

3. Fischer L., Bergmann F., Schimmack S., Hinz U., Prieß S., Müller-Stich BP, Werner J., Hackert T., Büchler MW. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg* 2014; 101: 1405-1412 [PMID: 25132004 DOI: 10.1002/bjs.9603]

4. Kleine M., Schrem H., Vondran FW., Kreek T., Klemmnauer J., Bektas H. Extended surgery for advanced pancreatic endocrine tumours. *Br J Surg* 2012; 99: 88-94 [PMID: 22135173 DOI: 10.1002/bjs.7681]

5. Asbun HJ, Stauffer JA. Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. *J Am Coll Surg* 2012; 215: 810-819 [PMID: 22999327 DOI: 10.1016/j.jamcollsurg.2012.08.006]

6. Cuschieri A., Jakimowicz JJ., van Spreuvel J. Laparoscopic distal 70% pancreatectomy and splenectomy for chronic pancreatitis. *Ann Surg* 1996; 223: 280-285 [PMID: 8604908 DOI: 10.1097/00000658-199603000-00008]

7. Gagner M., Pomp A., Herrera MF. Early experience with laparoscopic resections of islet cell tumors. *Surgery* 1996; 120:
Tsutsumi K, Kazanjian KK. Nonfunctional pancreatic neuroendocrine tumors in the United States.

Wong J, Parekh JR. Survival in resected pancreatic neuroendocrine tumors: a single-center experience.

Brunner SM, 10.1111/j.1477-2574.2009.00082.x. Pancreatic neuroendocrine neoplasms.

Ballian N, 10.1089/lap.2009.0412. Leads to long-term survival in patients with pancreatic endocrine tumors.

Postlewait LM, 10.1007/s00595-017-1485-y. Lymph node metastasis in pancreatic neuroendocrine tumor.

Sakata K, Okabe H, Nitta H, Hayashi H, Chikamoto A, Beppu T, Takamori H, Hirota M, Baba H. Significance of lymph node metastasis in pancreatic neuroendocrine tumor.

Assalia A, 10.1002/jhbp.47. Surgical resection of neuroendocrine tumors of the pancreas (pNETs) by minimally invasive surgery: the laparoscopic approach. Ann Surg Oncol 2012; 19: 1642-1651. [PMID: 21184115 DOI: 10.1002/jhbp.001-1456-5].

Shirotu T, Nagakawa Y, Sahara Y, Takishita C, Hijiikata Y, Hosokawa Y, Nakajima T, Osakabe H, Katsumata K, Tsuchida A. Surgical resection of neuroendocrine tumors of the pancreas (pNETs) by minimally invasive surgery: the laparoscopic approach. Gland Surg 2018; 7: 12-19. [PMID: 29629315 DOI: 10.21037/gs.2017.11.06].

Assalia A, Gagner M. Laparoscopic pancreatic surgery for islet cell tumors of the pancreas. World J Surg 2004; 28: 1239-1247. [PMID: 15517485 DOI: 10.1002/004-004-7617-8]

Han X, Xu J, Liu W. Clinicopathological characteristics and prognosis-related factors of resectable pancreatic neuroendocrine tumors: a retrospective study of 104 cases in a single Chinese center. Pancreas 2014; 43: 526-531. [PMID: 24658317 DOI: 10.1097/MPA.0000000000000065].

Taki K, Hashimoto D, Nakagawa S, Ozaki N, Tomiyasu S, Ohmura M, Arima K, Kaida T, Higashi T, Sakamoto K, Sakata K, Okabe H, Nitta H, Hayashi H, Chikamoto A, Beppu T, Takamori H, Hirota M, Baba H. Significance of lymph node metastasis in pancreatic neuroendocrine tumor. Surg Today 2017; 47: 1104-1110. [PMID: 28229300 DOI: 10.1007/s11605-017-1485-y].

Dimou AT, Syringos KN, Saif MW. Neuroendocrine tumors of the pancreas: what's new. Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22-24, 2010. JOP 2010; 11: 135-138. [PMID: 20208321].

Bonisexenga L, Panzuto F, Partelli S, Capelli P, Delle Fave G, Bettini R, Pederzoli P, Scarpa A, Falconi M. Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. Eur J Cancer 2012; 48: 1608-1615. [PMID: 22129889 DOI: 10.1016/j.ejca.2011.10.030].

Hashim YM, Trinka KM, Linehan DC, Strasberg SS, FIELDS RC, Cao D, Hawkins WG. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg 2014; 259: 197-203. [PMID: 24253141 DOI: 10.1097/SLA.0000000000000048].

Tsutsumi K, Ohtsuka T, Mori Y, Fujino M, Yasui T, Aishima S, Takahata S, Nakamura M, Ito T, Tanaka M. Analysis of lymph node metastasis in pancreatic neuroendocrine tumors (PNETs) based on the tumor size and hormonal production. J Gastroenterol 2012; 47: 678-685. [PMID: 22550698 DOI: 10.1007/s00535-012-0540-0].

Postlewait LM, Ethun CG, Baptiste GG, Le N, McMillin MR, Cardona K, Russell MC, Sarmiento JM, Kooby DA, Staley CA, Manhelh SK. Pancreatic neuroendocrine tumors: Preoperative factors that predict lymph node metastases to guide operative strategy. J Surg Oncol 2016; 114: 440-445. [PMID: 27334541 DOI: 10.1002/jso.24338].

Fendrich V, Langer P, Celik I, Bartisch DK, Zielke A, Ramaswamy A, Rothmund M. An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. Ann Surg 2006; 244: 845-51; discussion 852. [PMID: 17122609 DOI: 10.1097/01.sla.0000246951.21252.60].

Ballian N, Loeffler AG, Rajamanickam V, Norstedt PA, Weber SM, Cho CS. A simplified prognostic system for resected pancreatic neuroendocrine neoplasms. HPB (Oxford) 2009; 11: 422-428. [PMID: 19768147 DOI: 10.1111/j.1477-2574.2009.0082.x].

Brunner SM, Weber F, Werner JM, Agha A, Farkas SA, Schiltt HJ, Hornung M. Neuroendocrine tumors of the pancreas: a retrospective single-center analysis using the ENETS TNM-classification and immunohistochemical markers for risk stratification. BMC Surg 2015; 15: 49. [PMID: 25928025 DOI: 10.1186/s12893-015-0033-1].

Parikes JB, Wang SC, Bergsland EK, Venook AP, Warren RS, Kim GE, Nakakura EK. Lymph node sampling rates and predictors of nodal metastasis in pancreatic neuroendocrine tumor resections: the UCSF experience with 149 patients. Pancreas 2012; 41: 840-844. [PMID: 22781907 DOI: 10.1097/MPA.0b013e31823cada0].

Wong J, Fulp WJ, Strossberg JR, Kvol LS, Centeno BA, Hodul PJ. Predictors of lymph node metastases and impact on survival in resected pancreatic neuroendocrine tumors: a single-center experience. Am J Surg 2014; 208: 775-780. [PMID: 24997491 DOI: 10.1016/j.amjsurg.2014.04.003].

Gratian L, Pura J, Dinan M, roman S, Reed S, Sosa JA. Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. Ann Surg Oncol 2014; 3515-3521. [PMID: 24813437 DOI: 10.1245/s10434-014-3769-4].

Kazanjian KK, Reber HA, Hines OF. Resection of pancreatic neuroendocrine tumors: results of 70 cases. Arch Surg 2006; 141: 765-9; discussion 769. [PMID: 16924083 DOI: 10.1001/archsurg.141.8.765].

Tsutsumi K, Ohtsuka T, Fujino M, Nakashima H, Aishima S, Ueda J, Takahata S, nakamura M, Oda Y, Tanaka M. Analysis of risk factors for recurrence after curative resection of well-differentiated pancreatic neuroendocrine tumors based on the new grading classification. J Hepatobiliary Pancreat Sci 2014; 21: 418-425. [PMID: 24142395 DOI: 10.1002/jhp.472].

Birnbaum DJ, Turirini O, Ewald J, Barbier L, Aueret A, Hardwigen J, Brunet C, Moutardier V, Le Treut YP, Delpero JR.
Pancreatic neuroendocrine tumor: A multivariate analysis of factors influencing survival. *Eur J Surg Oncol* 2014; **40**: 1564-1571 [PMID: 25086992 DOI: 10.1016/j.ejso.2014.06.004]

32 Yoo YJ, Yang SJ, Hwang HK, Kang CM, Kim H, Lee WJ. Overestimated Oncologic Significance of Lymph Node Metastasis in G1 Nonfunctioning Neuroendocrine Tumor in the Left Side of the Pancreas. *Medicine (Baltimore)* 2015; **94**: e1404 [PMID: 26356692 DOI: 10.1097/MD.0000000000001404]

33 Partelli S, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A, Scarpa A, Ruszniewski P, Sauvanet A, Falconi M. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). *JAMA Surg* 2013; **148**: 932-939 [PMID: 23986355 DOI: 10.1001/jamasurg.2013.3376]

34 Nomura N, Fuji T, Kanazumi N, Takeda S, Nomoto S, Kasuya H, Sugimoto H, Yamada S, Nakao A. Nonfunctioning neuroendocrine pancreatic tumors: our experience and management. *J Hepatobiliary Pancreat Surg* 2009; **16**: 639-647 [PMID: 19365596 DOI: 10.1007/s00534-009-0099-1]

35 Kim MJ, Choi DW, Choi SH, Heo JS, Park HJ, Choi KK, Jung KT, Sung JY. Surgical strategies for non-functioning pancreatic neuroendocrine tumours. *Br J Surg* 2012; **99**: 1562-1568 [PMID: 23027073 DOI: 10.1002/bjs.8892]

36 Kuo EJ, Salem RR. Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. *Ann Surg Oncol* 2013; **20**: 2815-2821 [PMID: 23771245 DOI: 10.1245/s10434-013-3005-7]

37 Kishi Y, Shimada K, Nara S, Esaki M, Hiraoka N, Kosuge T. Basing treatment strategy for non-functional pancreatic neuroendocrine tumors on tumor size. *Ann Surg Oncol* 2014; **21**: 2882-2888 [PMID: 24740828 DOI: 10.1245/s10434-014-3701-y]

38 Conrad C, Kutlu OC, Dasari A, Chan JA, Vauthney JN, Adams DB, Kim M, Fleming JB, Katz MH, Lee JE. Prognostic Value of Lymph Node Status and Extent of Lymphadenectomy in Pancreatic Neuroendocrine Tumors Confined To and Extending Beyond the Pancreas. *J Gastrointest Surg* 2016; **20**: 1966-1974 [PMID: 27714644 DOI: 10.1007/s11605-016-3243-7]

39 Jiang Y, Jin JB, Zhan Q, Deng XX, Shen BY. Impact and Clinical Predictors of Lymph Node Metastases in Nonfunctional Pancreatic Neuroendocrine Tumors. *Chin Med J (Engli)* 2015; **128**: 3335-3344 [PMID: 26668149 DOI: 10.4103/0010-4679.171427]

40 Drymousis P, Raptis DA, Spalding D, Fernandez-Cruz L, Menon D, Breitenstein S, Davidson B, Frilling A. Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. *HPB (Oxford)* 2014; **16**: 397-406 [PMID: 24245906 DOI: 10.1111/hpb.12162]

41 DiNorcia J, Lee MK, Reavey PL, Genkinger JM, Lee JA, Schrope BA, Chabot JA, Allendorf JD. One hundred thirty resections for pancreatic neuroendocrine tumor: evaluating the impact of minimally invasive and parenchyma-sparing techniques. *J Gastrointest Surg* 2010; **14**: 1536-1546 [PMID: 20824378 DOI: 10.1007/s11605-010-1319-3]
