**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 55830

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Minimally invasive *vs* open pancreatectomy for nonfunctioning pancreatic neuroendocrine tumors**

Kim J *et al.* MIS *vs* open pancreatectomy for NFPNETs

Juwan Kim, Ho Kyoung Hwang, Woo Jung Lee, Chang Moo Kang

**Juwan Kim,** Department of Surgery, Yonsei University College of Medicine, Severance hospital, Seoul 03722, South Korea

**Ho Kyoung Hwang, Woo Jung Lee, Chang Moo Kang,** Department of Surgery, Yonsei University College of Medicine, Seoul 03722, South Korea

**Author contributions:** Kang CM designed the report; Kim J collected the patient’s clinical data, analyzed the data, and wrote the paper; Hwang HK and Lee WJ revised the paper for important intellectual content.

**Corresponding author: Chang Moo Kang, MD, PhD, Professor,** Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, Korea, Seoul 03722, South Korea. cmkang@yuhs.ac

**Received:** June 21, 2020

**Revised:** August 17, 2020

**Accepted:** September 14, 2020

**Published online:**

**Abstract**

BACKGROUND

The mainstay of treating nonfunctioning-pancreatic neuroendocrine tumors(NF-PNETs) is surgical resection. However, minimally invasive approaches to pancreatic resection for treating NF-PNETs are not widely accepted, and the long-term oncological outcomes of such approaches remain unknown.

AIM

To determine the short- and long-term outcomes of minimally invasive pancreatic resection conducted in patients with NF-PNETs.

METHODS

Prospective databases from Severance Hospital were searched for 110 patients who underwent curative resection for NF-PNETs between January 2003 and August 2018.

RESULTS

The proportion of minimally invasive surgery (MIS) procedures performed for NF-PNET increased to more than 75% after 2013. There was no significant difference in post-operative complications (*P* = 0.654), including pancreatic fistula (*P* = 0.890) and delayed gastric emptying (*P* = 0.652), between MIS and open approaches. No statistically significant difference was found in disease-free survival between the open approach group and the MIS group (median follow-up period, 28.1 mo; *P* = 0.428). In addition, the surgical approach (MIS *vs* open) was not found to be an independent prognostic factor in treating NF-PNET patients [Exp(β) = 1.062; *P* = 0.929].

CONCLUSION

Regardless of the type of surgery, a minimally invasive approach can be safe and feasible for select NF-PNET patients.

**Key Words:** Nonfunctioning-pancreas neuroendocrine tumor; Pancreatic neuroendocrine tumor; Minimally invasive surgery; Oncologic outcome; Laparoscopic pancreaticoduodenectomy; Laparoscopic distal pancreatectomy

Kim J, Hwang HK, Lee WJ, Kang CM. Minimally Invasive vs. Open Pancreatectomy for Nonfunctioning Pancreatic Neuroendocrine Tumors. *World J Gastrointest Oncol* 2020; In press

**Core Tip:** The mainstay of treating nonfunctioning-pancreatic neuroendocrine tumors (NF-PNETs) is surgical resection. However, minimally invasive approaches to pancreatic resection for treating NF-PNETs are not widely accepted and the long-term oncological outcomes of such approaches remain unknown. In this Long-term retrospective study with large numbers of subjects, there was no significant difference the short-term outcomes and recurrence rate of open resection and minimally invasive resection of NF-PNET.

**INTRODUCTION**

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms of the pancreas, which are produced by multipotent stem cells in the pancreatic ductal epithelium. PNETs comprise only 1%-2% of pancreatic neoplasms but their incidence is increasing[1]. Nonfunctioning (NF)-PNETs account for 15%-50% of PNETs, and their incidence may be increasing because of increased rates of incidental detection in imaging studies for other reasons[1].

The main method for treating PNETs is surgical resection. The resection of primary tumors in patients with PNETs is associated with improved survival across all disease stages[2,3]. Low-risk PNETs in the pancreas body and tail are ideally treated with minimally invasive surgery (MIS), which should be tailored to the individual patient[4]. Some studies have shown that laparoscopic distal pancreatectomy of NF-PNETs has comparable post-operative complications and oncological outcomes to an open approach[5-7]. However, minimally invasive approaches to pancreaticoduodenectomies and other types of surgery for treating NF-PNETs are not widely accepted, and the long-term oncological outcomes of such approaches remain unknown.

The objective of this study was to determine the short- and long-term outcomes of minimally invasive pancreatic resection performed in patients with NF-PNETs.

**MATERIALS AND METHODS**

***Data collection***

Prospective databases from Severance Hospital (Seoul, South Korea) were searched for patients who underwent curative resection for NF-PNETs between January 2003 and August 2018. Patients who underwent pancreatectomy in combination with resection were excluded. The Institutional Review Board approved this study (No. 4-2019-1136). Patients’ demographic, clinicopathologic and perioperative data were collected in an electronic medical record format and retrospectively reviewed. Patients who underwent distal pancreatectomy were defined as the distal-locating NF-PNET group; patients who underwent pylorus-preserving pancreaticoduodenectomy, central pancreatectomy, or total pancreatectomy for tumors located in the proximal part of the pancreas were defined as the proximal-locating NF-PNET group.

All surgeries were performed by specialized pancreatic surgeons. The decision of whether to conduct MIS or open surgery was mostly determined by tumor factors and surgeon’s preference. R0 resection was characterized as a minimum margin length > 1 mm. When there was no direct margin involvement by the tumor or such involvement was < 1 mm from the resection margin, such resections were classified as R1. Incomplete resection of all gross residual tumor structures was defined as an R2 resection[8]. Tumor location was classified by the center of the tumor. Tumor grade was evaluated according to World Health Organization (WHO) classifications, using data from final pathological reports[9]. Post-operative complications were classiﬁed using the Clavien-Dindo classiﬁcation system[10]. Post-operative pancreatic ﬁstulae were deﬁned according to the definition created by the International Study Group of Pancreatic Fistula (commonly known as the ISGPF)[11]. Delayed gastric emptying was also defined according to the definition by the International Study Group of Pancreatic Surgery[12]. Disease recurrence was defined as suspicious image findings during post-operative surveillance. The duration of disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence.

***Statistical analysis***

SPSS (version 22.0; IBM Corp., Armonk, NY, United States) and R 3.3.3 software was used to conduct statistical analyses. Numerical variables are presented as medians with interquartile ranges, and the group results were compared with the Student’s *t*-test or Mann-Whitney *U* test. Nominal variables are expressed as values and percentages and compared with the results of the chi-squared or Fisher’s exact test. Recurrence probabilities were estimated using Kaplan-Meier methodology and compared by log-rank analysis. Potential risk factors associated with tumor recurrence were analyzed using univariate and multivariate cox hazard regression models. To evaluate the correlation of tumor recurrence with MIS and open approaches, variables that were found to be associated with overall survival on univariate cox analysis and MIS were included in a multivariate cox proportional model. In all analyses, a two-tailed *P*-value less than 0.05 was considered to be statistically significant.

**RESULTS**

***General patient characteristics***

Between January 2003 and August 2018, a total of 110 patients underwent curative resection for NF-PNETs. Forty-eight patients (43.6%) underwent open curative resection, sixty-two (56.4%) minimally invasive curative resection, forty-seven laparoscopic curative resection (42.7%), and fifteen robot-assisted (13.6%) curative resection. Over the 15-year analysis period, the proportion of minimally invasive approaches increased to approximately 75% after 2013 (before 2007: 0%; 2007-2009: 16.7%; 2010-2012: 31.8%; 2013-2015: 77.5%; 2016-2018: 76.7%, *P* = 0.001, Figure 1).

The median age of the 110 patients who underwent curative resection for NF-PNETs was 56.0 years (range: 46.0-63.0 years), with more female patients than male patients (*n* = 59, 53.6%). Fifty-one (46.4%) patients underwent distal pancreatectomy, twenty-two (20.0%) enucleation, seven (6.4%) central pancreatectomy, twenty-one (19.1%) pylorus-preserving pancreaticoduodenectomy, and nine (8.2%) total pancreatectomy. The median tumor size was 1.8 cm (range: 1.2-3.2 cm). Approximately three-quarters of patients (*n* = 78, 70.9%) were grade 1 according to the 2010 WHO classification, 27 (24.54%) were grade 2, and 4 (3.63%) were grade 3. One patient (0.9%) who underwent open central pancreatectomy in 1993 could not be defined according to the 2010 WHO classification, due to the lack of mitotic counts and other information in the final pathological reports. After surgery, approximately 50% of patients experienced complications, of whom 9 (8.1%) experienced severe complications, defined as Clavien-Dindo grades III–IV. The median length of patient stay in the hospital was 11.5 d (range: 8.0-17.0 d). The clinicopathological characteristics and surgical details of NF-PNET patients are given in Table 1.

***Comparative analysis of open and minimally invasive approaches in terms of distal locations of NF-PNETs***

A comparison of the clinicopathological characteristics and surgical details of distal pancreatectomy are given in Table 2. Overall, there were no significantly different perioperative clinical parameters between the open distal pancreatectomy group and the minimally invasive distal pancreatectomy group (*P* > 0.05). Complication rates also did not differ significantly between groups (*P* = 0.729). In addition, the occurrence of post-operative pancreatic fistulae also did not differ significantly between groups. However, the minimally invasive distal pancreatectomy group tended to have a shorter average post-operative length of stay (8.0 d) than the open distal pancreatectomy group (14.0 d, *P* < 0.001). There were no significantly difference in the number of lymph node sampling between the open group and the minimally invasive group (*P* = 0.767).

***Comparative analysis of open and minimally invasive approaches in terms of proximal locations of NF-PNETs***

Of the 110 patients, 37 were in the proximal location NF-PNET group, and 21 underwent pylorus-preserving pancreaticoduodenectomy (57%), 7 (19%) central pancreatectomy, and 9 (27%) total pancreatectomy because the tumor was located on the proximal part or involved the whole pancreas.

In the comparative analysis, there was no significant difference in the average rates of post-operative complications, including post-operative pancreatic fistulae and delayed gastric emptying, between the open and MIS groups (Table 3). The average length of post-operative stay did not significantly differ between the open group (20.0 d) and the MIS group (13.0 d) (*P* = 0.210). However, the average body mass index (referred to as BMI) of the open group (24.6) was significantly higher than that of the MIS group (21.9) (*P* = 0.006). The MIS group had a longer average operation time (512 min) than the open group (346 min) (*P* < 0.001). The average pathological tumor size (1.5 cm) was significantly smaller in the MIS group than in the open group (2.6 cm, *P* = 0.041). There were no significantly difference in the number of lymph node sampling between the open group and the minimally invasive group (*P* = 0.804).

***Long-term oncological outcomes of NF-PNET resections***

After a median follow-up period of 28.1 mo (range: 11.3–53.0 mo), 12 patients (10.9%) experienced recurrence (Open: 16.7%, MIS: 6.5%). Comparative analysis showed that there was no statistically significant difference in DFS rates between the open group and the MIS group (*P* = 0.428, Figure 2). In a subgroup analysis of distal location of NF-PNETs, with a median follow-up period of 22.1 mo (range: 10.7-41.3), 7 (13.7%) of the 51 patients who underwent distal pancreatectomy experienced recurrence (Open: 25%, MIS: 10.3%). There was no significant difference in DFS rates between the open and MIS groups (*P* = 0.418). In addition, with a median follow-up period of 31.8 mo (range: 10.0–41.3 mo), 5 (13.5%) of the 37 patients, who had proximally located NF-PNETs, experienced recurrence. There were also no significant differences in terms of DFS rates between the Open and MIS groups for treatment of proximally located NF-PNETs (*P* = 0.178).

Univariate analysis showed that tumor size > 2.5 cm [hazard ratio (HR): 22.21, 95%CI: 2.86-172.69; *P* = 0.003], 2010 WHO classification of G3 (HR: 71.55, 95%CI: 6.43-795.75; *P* = 0.001), and lympho-vascular invasion (HR: 8.77, 95%CI: 2.75-27.93; *P* < 0.001) were associated with tumor recurrence. Multivariate analysis also showed that these factors were associated with tumor recurrence. However, surgical approach, namely either MIS or open, was not associated with tumor recurrence (Table 4, Figure 2).

**DISCUSSION**

The current study showed that there was no significant difference in the short- and long-term outcomes of open resection and MIS. The surgical approach was not found to be an independent prognostic factor in treating NF-NET patients.

Since Gumbs *et al*[13] (2008) reported that minimally invasive distal pancreatectomy had shorter surgical durations and lengths of hospital stay than open distal pancreatectomy and similar levels of post-operative complications and oncological outcomes, many centers that perform laparoscopic distal pancreatectomies on PNET patients have shown the feasibility of a laparoscopic approach and its relative safety compared to open resection[14-16]. Laparoscopic distal pancreatectomies have similar oncological outcomes and levels of post-operative complications as open distal pancreatectomies but shorter hospital stays[6,7,17]. The other study also showed that robotic assisted distal pancreatectomy and laparoscopic distal pancreatectomy were similar in post-operative complication and long term outcomes[18]. Some studies have also been conducted in functional-PNET and NF-PNET patients. The current study was conducted with NF-PNET patients only, but its results were similar to those on distal pancreatectomies.

Previous studies showed lymph node metastasis in pNET indicated poor prognosis[19,20]. However a study have suggested that routine conventional distal pancreatectomies with splenectomies to retrieve regional lymph nodes may be too extensive for NF-PNET patients with 2010 WHO classification grade 1[21]. In this study, there are no significant difference between MIS and open approach in nodal harvest. Thus, minimally invasive distal pancreatectomies are a feasible and safe method for treating NF-PNET patients.

Some studies have compared minimally invasive and open pancreatic resections to other types of pancreatic resections for PNETs. One study showed that a minimally invasive approach and parenchyma-sparing techniques for treating PNETs did not increase morbidity or reduce survival rates[22]. In addition, other studies showed that minimally invasive and parenchyma-sparing operations were associated with shorter hospital stays[23,24,25]. However, that study did not compare the minimally invasive approach and open resection but rather compared traditional pancreatic resection and minimally invasive approaches with parenchyma-sparing techniques (central pancreatectomy, enucleation). In this study, in proximal pancreatic resections, including central pancreatectomies, pancreaticoduodenectomies and total pancreatectomies, open and minimally invasive resections had similar levels of post-operative complications. There was no difference between the rates of post-operative pancreatic fistulae. PNET patients had high risks of forming post-operative pancreatic fistulae, because the pancreas is soft and its ducts have small diameters[26]. Large tumor size, poor differentiation, and lympho-vascular invasion are associated with NF-PNET tumor recurrence in this study and other study[27]. The diagnosis and treatment of NF-PNETs may be slow because of its rarity[28]. Delayed diagnosis and treatment of PNETs are associated with more advanced tumor characteristics and higher recurrence rates[29]. The early diagnosis of PNETs is an important component of good prognoses for NF-PNET patients.

In this study, BMI and pathological tumor size in the Open and MIS groups differed for proximal pancreatic resections. The baseline characteristics of the groups may have differed because the resection approach was determined by tumor factors and surgeon’s preference. Other studies have suggested criteria for selecting a minimally invasive approach to treat left-sided pancreatic cancer[16,30]. The criteria used to select resected PNET patients may help improve the prognosis of the minimally invasive approach. In the current study, there was no difference in length of hospital stay between the minimally invasive approach group and the open resection group for proximal pancreatic resections. However, several studies have shown that a minimally invasive approach to pancreatic resection is strongly correlated with shorter hospital stays[6,7]. The fact that the current study showed no differences between groups may be a product of patient heterogeneity.

This study had several limitations. Despite its large sample size, it was based upon a retrospective review of patient data and analyzed patients from a single center. Most of the patients who underwent a minimally invasive approach were diagnosed after 2007, so they had shorter follow-up durations than the open pancreatic resection group. As the skills of pancreatic surgeons improve in using a minimally invasive approach, surgical duration, intra-operative bleeding amount, post-operative complication rates, conversion rates, and long-term outcomes are expected to differ over time. Surgeons chose whether to apply a minimally invasive approach, and subgroup analysis showed that the open pancreatic resection group had more advanced tumor features and a higher BMI than the MIS group. In the current study, minimally invasive approaches included laparoscopic and robotic approaches, so future studies should compare these approaches for the treatment of PNET patients.

**CONCLUSION**

The proportion of minimally invasive approaches for the treatment of NF-PET has increased to more than 75%. There were no significant differences in the short- and long-term outcomes between open resection and minimally invasive distal pancreatectomy for the treatment of NF-PNET patients. Minimally invasive approaches including pylorus-preserving pancreaticoduodenectomies, central pancreatectomies, and total pancreatectomies had comparable post-operative complication rates and short-term outcomes. Regardless of the type of surgery, a minimally invasive approach may be safe and feasible for selected NF-PNET patients undergoing pancreatic resection.

**ARTICLE HIGHLIGHTS**

***Research background***

The mainstay of treatment for nonfunctioning (NF)-pancreatic neuroendocrine tumors (PNETs) is surgical resection. Minimally invasive approaches to pancreatic resection are not yet widely accepted as NF-PNET treatment.

***Research motivation***

Some studies have shown laparoscopic distal pancreatectomy of NF-PNETs as producing post-operative complications and oncological outcomes that are comparable to the open approach. However, the long-term oncological outcomes of minimally invasive approaches to pancreaticoduodenectomies and other types of surgery for treating NF-PNETs remain unknown.

***Research objectives***

The current study was designed to determine the short- and long-term outcomes of minimally invasive pancreas resection conducted on patients with NF-PNETs.

***Research methods***

Severance Hospital’s prospective databases were searched for patients who underwent curative resections for NF-PNETs between January 2003 and August 2018. Patients who underwent pancreatectomy in combination with resection were excluded.

***Research results***

Groups of patients who underwent proximal pancreas resections (central pancreatectomies, pancreaticoduodenectomies, and total pancreatectomies), open resection, and minimally invasive resection showed similar levels of post-operative complications. The groups showed no difference between the rates of post-operative pancreatic fistulae. However, PNET patients showed high risk of forming post-operative pancreatic fistulae, due to the softness of the pancreas and small diameter of its ducts. Large tumor size, poor differentiation, and lympho-vascular invasion were associated with NF-PNET tumor recurrence.

***Research conclusions***

Minimally invasive approaches of pylorus-preserving pancreaticoduodenectomy, central pancreatectomy, and total pancreatectomy led to comparable post-operative complication rates and short-term outcomes. The type of surgical approach (minimally invasive *vs* open) was not an independent prognostic factor in treating NF-PNET patients [Exp(β) = 1.062, *P* = 0.929]. Regardless of the type of surgery, a minimally invasive approach could be safe and feasible for select NF-PNETs patients who are undergoing pancreas resection.

***Research perspectives***

The current study of minimally invasive pancreatic surgeries collectively evaluated laparoscopic and robotic approaches. Future studies should involve comparison of the two ¾ laparoscopic *vs* robotic ¾ in treating PNET patients. Furthermore, use of the latest criteria to select resected PNET patients may help improve prognosis of the minimally invasive approach.

**REFERENCES**

1 **Anderson CW**, Bennett JJ. Clinical Presentation and Diagnosis of Pancreatic Neuroendocrine Tumors. *Surg Oncol Clin N Am* 2016; **25**: 363-374 [PMID: 27013370 DOI: 10.1016/j.soc.2015.12.003]

2 **Hill JS**, McPhee JT, McDade TP, Zhou Z, Sullivan ME, Whalen GF, Tseng JF. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. *Cancer* 2009; **115**: 741-751 [PMID: 19130464 DOI: 10.1002/cncr.24065]

3 **Kang CM**, Kim KS, Choi JS, Lee WJ, Kim BR. Experiences with nonfunctioning neuroendocrine neoplasms of the pancreas. *Dig Surg* 2005; **22**: 453-458 [PMID: 16543738 DOI: 10.1159/000092011]

4 **D'Haese JG**, Tosolini C, Ceyhan GO, Kong B, Esposito I, Michalski CW, Kleeff J. Update on surgical treatment of pancreatic neuroendocrine neoplasms. *World J Gastroenterol* 2014; **20**: 13893-13898 [PMID: 25320524 DOI: 10.3748/wjg.v20.i38.13893]

5 **Cienfuegos JA**, Salguero J, Núñez-Córdoba JM, Ruiz-Canela M, Benito A, Ocaña S, Zozaya G, Martí-Cruchaga P, Pardo F, Hernández-Lizoáin JL, Rotellar F. Short- and long-term outcomes of laparoscopic organ-sparing resection in pancreatic neuroendocrine tumors: a single-center experience. *Surg Endosc* 2017; **31**: 3847-3857 [PMID: 28127714 DOI: 10.1007/s00464-016-5411-y]

6 **Han SH**, Han IW, Heo JS, Choi SH, Choi DW, Han S, You YH. Laparoscopic versus open distal pancreatectomy for nonfunctioning pancreatic neuroendocrine tumors: a large single-center study. *Surg Endosc* 2018; **32**: 443-449 [PMID: 28664429 DOI: 10.1007/s00464-017-5702-y]

7 **Zhang XF**, Lopez-Aguiar AG, Poultsides G, Makris E, Rocha F, Kanji Z, Weber S, Fields R, Krasnick BA, Idrees K, Smith PM, Cho C, Schmidt CR, Maithel SK, Pawlik TM; United States Neuroendocrine Tumor Study Group. Minimally invasive versus open distal pancreatectomy for pancreatic neuroendocrine tumors: An analysis from the U.S. neuroendocrine tumor study group. *J Surg Oncol* 2019; **120**: 231-240 [PMID: 31001868 DOI: 10.1002/jso.25481]

8 Standards and Minimum Datasets for Reporting Cancers. Minimum Dataset for the Histopathological Reporting of Pancreatic, Ampulla of Vater and Bile Duct Carcinoma. London, UK: The royal college of pathologists, 2019

9 **Klöppel G**, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y AcadSci* 2004; **1014**: 13-27 [PMID: 15153416 DOI: 10.1196/annals.1294.002]

10 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.a]

11 **Bassi C**, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8-13 [PMID: 16003309 DOI: 10.1016/j.surg.2005.05.00]

12 **Wente MN**, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]

13 **Gumbs AA**, Grès P, Madureira F, Gayet B. Laparoscopic vs open resection of pancreatic endocrine neoplasms: single institution's experience over 14 years. *Langenbecks Arch Surg* 2008; **393**; 391-395 [PMID: 18196267 DOI: 10.1007/s00423-007-0255-5]

14 **Xourafas D**, Tavakkoli A, Clancy TE, Ashley SW. Distal pancreatic resection for neuroendocrine tumors: is laparoscopic really better than open? *J Gastrointest Surg* 2015; **19**: 831-840 [PMID: 25759075 DOI: 10.1007/s11605-015-2788-]

15 **Ishida H**, Lam AK. Pancreatic neuroendocrine neoplasms: The latest surgical and medical treatment strategies based on the current World Health Organization classification. *Crit Rev OncolHematol* 2020; **145**: 102835 [PMID: 31864179 DOI: 10.1016/j.critrevonc.2019.102835]

16 **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]

17 **Hu BY**, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. *World J Gastroenterol* 2016; **22**: 7797-7805 [PMID: 27678363 DOI: 10.3748/wjg.v22.i34.7797]

18 **Alfieri S**, Butturini G, Boggi U, Pietrabissa A, Morelli L, Vistoli F, Damoli I, Peri A, Fiorillo C, Pugliese L, Ramera M, De Lio N, Di Franco G, Esposito A, Landoni L, Rosa F, Menghi R, Doglietto GB, Quero G; Italian Robotic pNET Group. Short-term and long-term outcomes after robot-assisted versus laparoscopic distal pancreatectomy for pancreatic neuroendocrine tumors (pNETs): a multicenter comparative study. *Langenbecks Arch Surg* 2019; **404**: 459-468 [PMID: 31055639 DOI: 10.1007/s00423-019-01786-x]

19 **Boninsegna L**, Panzuto F, Partelli S, Capelli P, DelleFave 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]

20 **Hashim YM**, Trinkaus 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.0000000000000348]

21 **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]

22 **Paiella S**, De Pastena M, Korrel M, Pan TL, Butturini G, Nessi C, De Robertis R, Landoni L, Casetti L, Giardino A, Busch O, Pea A, Esposito A, Besselink M, Bassi C, Salvia R. Long term outcome after minimally invasive and open Warshaw and Kimura techniques for spleen-preserving distal pancreatectomy: International multicenter retrospective study. *Eur J SurgOncol* 2019; **45**: 1668-1673 [PMID: 31005470 DOI: 10.1016/j.ejso.2019.04.004]

23 **Gharios J**, Hain E, Dohan A, Prat F, Terris B, Bertherat J, Coriat R, Dousset B, Gaujoux S. Pre- and intraoperative diagnostic requirements, benefits and risks of minimally invasive and robotic surgery for neuroendocrine tumors of the pancreas. *Best Pract Res Clin Endocrinol Metab* 2019; **33**: 101294 [PMID: 31351817 DOI: 10.1016/j.beem.2019.101294]

24 **Weilin M**, Xu H, Yang L, Wenqi C, Huanyu W, Wentao Z, Dayong J, Wenchuan W, Dansong W, Tiantao K, Lei Z, Wenhui L, Xuefeng X. Propensity score-matched analysis of clinical outcome after enucleation versus regular pancreatectomy in patients with small non-functional pancreatic neuroendocrine tumors. *Pancreatology* 2020; **20**: 169-176 [PMID: 31941586 DOI: 10.1016/j.pan.2019.12.007]

25 **Memeo R**, Roselli S, Lupo L, Cherkaoui Z, Pessaux P. Laparoscopic management of neuroendocrine tumors: state-of-the-art. *Transl Gastroenterol Hepatol* 2017; **2**: 109 [PMID: 29354766 DOI: 10.21037/tgh.2017.11.19]

26 **Andreasi V**, Muffatti F, Guarneri G, Falconi M, Partelli S. Surgical Principles in the Management of Pancreatic Neuroendocrine Neoplasms. *Curr Treat Options Oncol* 2020; **21**: 48 [PMID: 32350693 DOI: 10.1007/s11864-020-00736-w]

27 **Assi HA**, Mukherjee S, Kunz PL, Machiorlatti M, Vesely S, Pareek V, Hatoum H. Surgery Versus Surveillance for Well-Differentiated, Nonfunctional Pancreatic Neuroendocrine Tumors: An 11-Year Analysis of the National Cancer Database. *Oncologist* 2020; **25**: e276-e283 [PMID: 32043766 DOI: 10.1634/theoncologist.2019-0466]

28 **Kang CM**, Park SH, Kim KS, Choi JS, Lee WJ, Kim BR. Surgical experiences of functioning neuroendocrine neoplasm of the pancreas. *Yonsei Med J* 2006; **47**: 833-839 [PMID: 17191313 DOI: 10.3349/ymj.2006.47.6.833]

29 **Lee L**, Ito T, Jensen RT. Prognostic and predictive factors on overall survival and surgical outcomes in pancreatic neuroendocrine tumors: recent advances and controversies. *Expert Rev Anticancer Ther* 2019; **19**: 1029-1050 [PMID: 31738624 DOI: 10.1080/14737140.2019.1693893]

30 **Lee SH**, Hwang HK, Kang CM, Lee WJ. The Yonsei criteria as a clinically detectable parameter for excellent prognosis in resected left-sided pancreatic cancer: outcomes of a propensity score-matched analysis. *Surg Endosc* 2017; **31**: 4656-4664 [PMID: 28389802 DOI: 10.1007/s00464-017-5529-6]

**Footnotes**

**Institutional review board statement:** This study was approved by the Ethics Committee of the Yonsei University Health System, Severance Hospital, Institutional Review Board (No. 4-2019-1136).

**Informed consent statement:** The Hospital’s Institutional Review Board waived the requirement for informed consent in accordance with the retrospective nature of the study.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Data sharing statement:** Data requests should be directed to juwankim1717@yuhs.ac.

**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: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** June 21, 2020

**First decision:** July 30, 2020

**Article in press:**

**Specialty type:** Surgery

**Country/Territory of origin:** South Korea

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

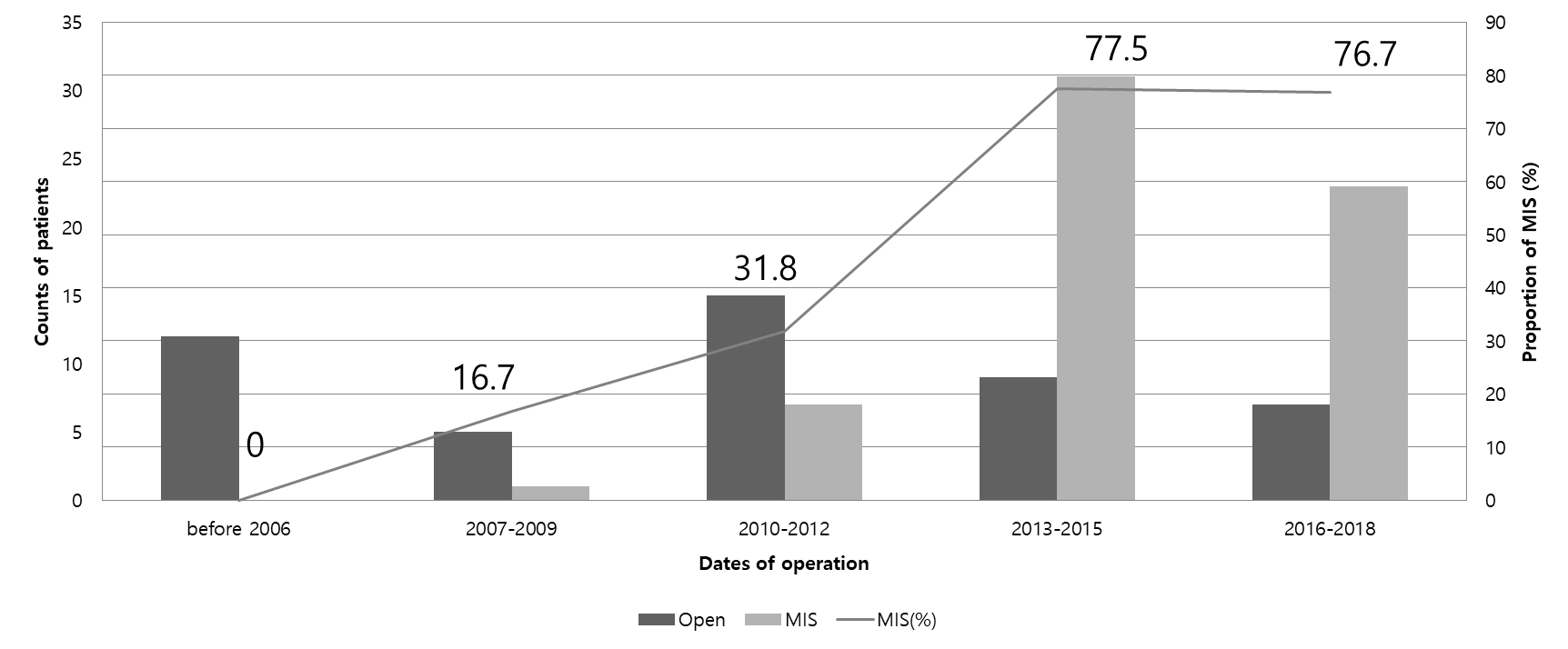
Grade C (Good): C

Grade D (Fair): 0

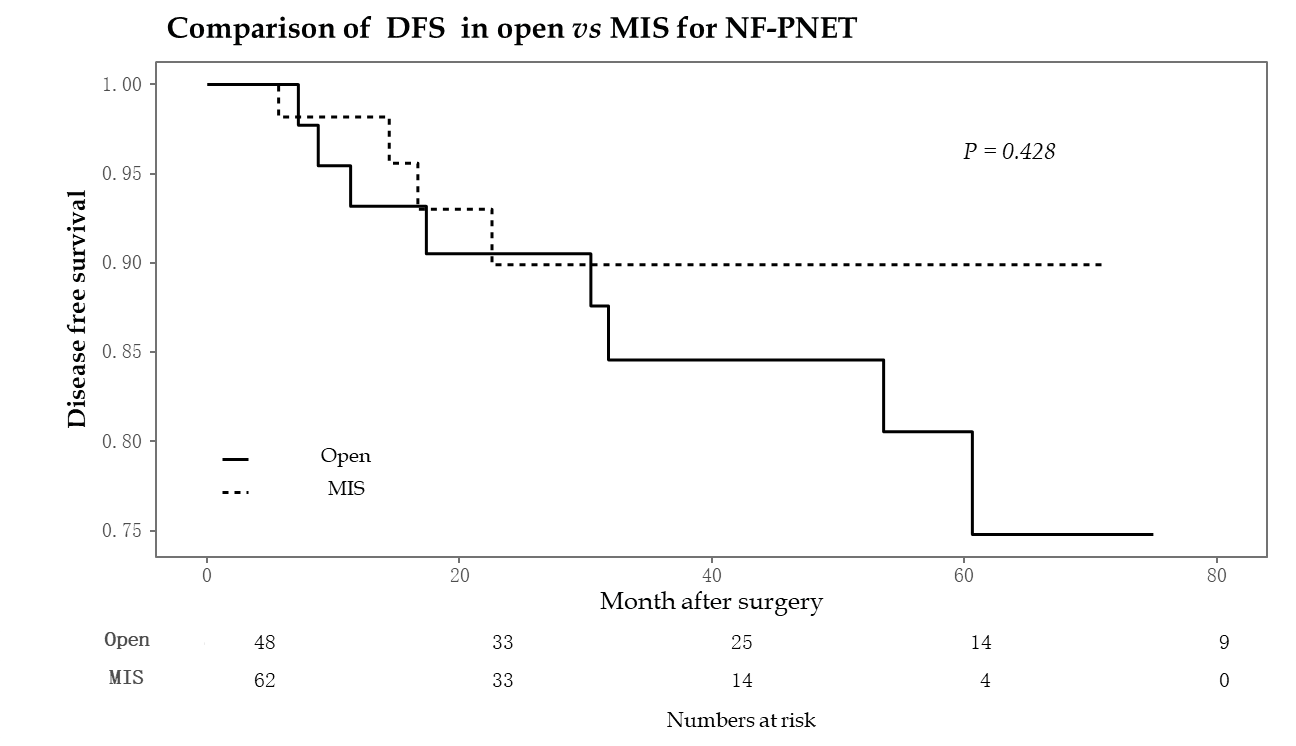
Grade E (Poor): 0

**P-Reviewer:** Wada Y **S-Editor:** Zhang H **L-Editor: P-Editor:**

**Figure legends**



**Figure 1 Changes in surgical approaches for treating nonfunctioning-pancreatic neuroendocrine tumors over time.** MIS: Minimally invasive surgery.

****

**Figure 2 Comparison of disease-free survival rates between open pancreatic resection and minimally invasive approaches for treating patients with nonfunctioning pancreatic neuroendocrine tumors.** DFS: Disease-free survival; MIS: Minimally invasive surgery; NF-PNET: Nonfunctioning-pancreatic neuroendocrine tumors.

**Table 1 Clinicopathological characteristics of resected nonfunctioning pancreatic neuroendocrine tumors**

|  |  |
| --- | --- |
| **Variable** | **Finding** |
| Age in yr, median (range) | 56.0 (46.0–63.0) |
| Male, *n* (%) | 51 (46.4) |
| BMI in kg/m², median (range) | 24.1 (22.1–26.3) |
| ASA, grade, *n* (%) |  |
| I | 30 (27.3) |
| II | 59 (53.6) |
| III | 21 (19.1) |
| Diabetes, preoperative, *n* (%) | 20 (18.2) |
| Pancreatic tumor location, *n* (%) |  |
| Head | 41 (35.7) |
| Neck | 6 (5.2) |
| Body | 26 (22.6) |
| Tail | 42 (36.5) |
| Type of surgery, *n* (%) |  |
| Distal pancreatectomy | 51 (46.4) |
| Enucleation | 22 (20.0) |
| Central pancreatectomy | 7 (6.4) |
| Pylorus-preservingpancreaticoduodenectomy | 21 (19.1) |
| Total pancreatectomy | 9 (8.2) |
| MIS or open, *n* (%) |  |
| MIS | 62 (56.4) |
| Open | 48 (43.6) |
| Post-operative length of stay in d, median (range) | 11.5 (8.0–17.0) |
| Clavien-Dindo grade, *n* (%) |  |
| 0: no complications | 58 (52.7) |
| I | 35 (31.8) |
| II | 8 (7.3) |
| IIIa | 5 (4.5) |
| IIIb | 3 (2.7) |
| IVa | 1 (0.9) |
| IVb | 0 (0) |
| POPF by ISGPF |  |
| Grade A | 47 (40.9%) |
| Grade B | 6 (5.2%) |
| Grade C | 0 (0%) |
| DGE by ISGPS |  |
| Grade A | 18 (15.7%) |
| Grade B | 1 (0.9%) |
| Grade C | 0 (0%) |
| Resection margin status, *n* (%) |  |
| R0 | 97 (88.2) |
| R1 | 5 (4.5) |
| R2 | 8 (7.3) |
| Pathological tumor size in cm, median (range) | 1.8 (1.2–3.2) |
| T stage by ENETS classification |  |
| T1 | 56 (50.9%) |
| T2 | 18 (16.4%) |
| T3 | 36 (32.7%) |
| T4 | 0 (0.0%) |
| N status |  |
| Negative | 57 (51.9%) |
| Positive | 9 (8.1%) |
| No lymphadenectomy | 44 (40.0%) |
| Metastasis present, *n* (%) | 5 (4.5) |
| 2010 WHO classification grade, *n* (%) |  |
| G1 | 78 (70.9) |
| G2 | 27 (24.54) |
| G3 | 4 (3.63) |
| Unknown | 1 (0.9) |

ASA: American Society of Anesthesiologists; BMI: Body mass index; DGE: Delayed gastric emptying; ENETS: European Neuroendocrine Tumor Society; ISGPS: International Study Group on Pancreatic Surgery; ISGPF: International Study Group on Pancreatic Fistula; POPF: Post-operative pancreatic ﬁstulae; WHO: World Health Organization.

**Table 2 Clinicopathological characteristics of minimally invasive and open approaches in terms of the distal location of nonfunctioning pancreatic neuroendocrine tumors**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Open approach, *n* = 12** | **MIS, *n* = 39** | ***P* value** |
| Male | 7 (58.3%) | 19 (48.7%) | 0.801 |
| Age in yr, median (range) | 58.5 (51.0-64.5) | 56.0 (47.0-64.5) | 0.617 |
| BMI in kg/m², median (range) | 24.6 (22.1-25.5) | 24.8 (22.9-27.3) | 0.418 |
| ASA grade, *n* (%) |  |  | 0.243 |
| Ⅰ | 5 (41.7) | 7 (17.9) |  |
| Ⅱ | 5 (41.7) | 23 (59.0) |  |
| Ш | 2 (16.7) | 9 (23.1) |  |
| Spleen-preserving distal pancreatectomy | 5 (41.7%) | 26 (66.6%) |  |
| Conversion, *n* (%) | - | 4 (10.2) |  |
| Robot-assisted | - | 8 (20.5%) |  |
| Operative time as minimum, median (range) | 179.0 (159.5–251.5) | 216.0 (185.5–276.0) | 0.105 |
| Blood loss in cc, median (range) | 175.0 (65.0–450.0) | 100 (45.0–275.0) | 0.093 |
| Clavien-Dindo grade |  |  | 0.729 |
| 0: no complications | 7 (58.3%) | 26 (66.7%) |  |
| I | 4 (33.3%) | 10 (25.6%) |  |
| II | 1 (8.3%) | 2 (5.1%) |  |
| IIIa | 0 (0.0%) | 1 (2.6%) |  |
| DGE by ISGPS |  |  | 0.561 |
| Grade A | 0 (0.0%) | 4 (10.3%) |  |
| Grade B | 0 (0.0%) | 0 (0.0%) |  |
| Grade C | 0 (0.0%) | 0 (0.0%) |  |
| POPF by ISGPF |  |  | 0.805 |
| Grade A | 7 (58.3%) | 20 (51.3%) |  |
| Grade B | 0 (0.0%) | 1 (2.6%) |  |
| Grade C | 0 (0.0%) | 0 (0.0%) |  |
| Post-operative length of stay in d, median (range) | 14.0 (11.5-16.0) | 8.0 (7.0-10.5) | < 0.001 |
| Resection margin status |  |  | 0.612 |
| R0 | 12 (100.0%) | 36 (92.3%) |  |
| R1 | 0 (0.0%) | 2 (5.1%) |  |
| R2 | 0 (0.0%) | 1 (2.6%) |  |
| Pathological tumor size in cm, median (range) | 2.5 (1.4-3.9) | 2.0 (1.5-3.2) | 0.548 |
| T stage by ENETS classification |  |  | 0.563 |
| T1 | 5 (41.7%) | 20 (51.3%) |  |
| T2 | 2 (16.7%) | 9 (23.1%) |  |
| T3 | 5 (41.7%) | 10 (25.6%) |  |
| N stage |  |  | 0.056 |
| Negative | 9 (75.0%) | 38 (97.4%) |  |
| Positive | 3 (25.0%) | 1 (2.6%) |  |
| M stage |  |  |  |
| 0 | 12 (100.0%) | 39 (100.0%) |  |
| Nodal harvest, median (range) | 0.0 (0.0-5.5) | 1.0 (0.0-3.5) | 0.767 |
| 2010 WHO grade |  |  | 0.365 |
| G1 | 7 (57.1%) | 25 (64.1%) |  |
| G2 | 4 (42.9%) | 14 (35.9%) |  |
| G3 | 1 (8.3%) | 0 (0%) |  |

ASA: American Society of Anesthesiologists; BMI: Body mass index; DGE: Delayed gastric emptying; ENETS: European Neuroendocrine Tumor Society; ISGPS: International Study Group on Pancreatic Surgery; ISGPF: International Study Group on Pancreatic Fistula; MIS: Minimally invasive surgery; POPF: Post-operative pancreatic ﬁstulae; WHO: World Health Organization.

**Table 3 Clinicopathological characteristics of the minimally invasive surgery and open groups in terms of the proximal location of nonfunctioning pancreatic neuroendocrine tumors**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Open, *n* =22** | **MIS, *n* =15** | ***P* value** |
| Male | 11 (50.0%) | 5 (33.3%) | 0.505 |
| Age in yr, median (range) | 53.5 (40.0–65.0) | 53.0 (43.0–65.5) | 0.631 |
| BMI in kg/m², median (range) | 24.6 (22.7–27.3) | 21.9 (21.1–23.4) | 0.006 |
| ASA grade, *n* (%) |  |  | 0.069 |
| I | 6 (27.3) | 0 (0.0) |  |
| II | 14 (63.6) | 12 (80.0) |  |
| III | 2 (9.1) | 3 (20.0) |  |
| Type of surgery |  |  | 0.541 |
| Central pancreatectomy | 3 (13.6%) | 4 (26.7%) |  |
| PPPD | 14 (63.6%) | 7 (46.7%) |  |
| Total pancreatectomy | 5 (22.7%) | 4 (26.7%) |  |
| Operative time in min, median (range) | 346.0 (295.0-400.0) | 512.0 (462.5-530.0) | < 0.001 |
| Blood loss in cc, median (range) | 450.0 (100.0-1020.0) | 400. (175.0-450.0) | 0.515 |
| Clavien-Dindo grade |  |  | 0.489 |
| 0: no complications | 10 (45.5%) | 4 (26.7%) |  |
| I | 8 (36.4%) | 5 (33.3%) |  |
| II | 1 (4.5%) | 3 (20.0%) |  |
| IIIa | 1 (4.5%) | 1 (6.7%) |  |
| IIIb | 2 (9.1%) | 1 (6.7%) |  |
| IV | 0 (0.0%) | 1 (6.7%) |  |
| DGEby ISGPS |  |  | 0.457 |
| Grade A | 7 (31.8%) | 5 (33.3%) |  |
| Grade B | 0 (0.0%) | 1 (6.7%) |  |
| Grade C | 0 (0.0%) | 0 (0.0%) |  |
| POPF by ISGPF |  |  | 0.571 |
| Grade A | 5 (22.7%) | 4 (26.7%) |  |
| Grade B | 1 (4.5%) | 2 (13.3%) |  |
| Grade C | 0 (0.0%) | 0 (0.0%) |  |
| Post-operative length of stay in d, median (range) | 20.0 (14.0–30.0) | 13.0 (10.5–24.5) | 0.210 |
| Resection margin status |  |  | 0.505 |
| R0 | 20 (90.9%) | 15 (100.0%) |  |
| R1 | 0 (0.0%) | 0 (0.0%) |  |
| R2 | 2 (9.1%) | 0 (0.0%) |  |
| Pathological tumor size incm, median (range) | 2.6 (1.5-4.5) | 1.5 (1.3-2.2) | 0.041 |
| T stage by ENETs classification |  |  | 0.081 |
| T1 | 6 (27.3%) | 8 (53.3%) |  |
| T2 | 5 (22.7%) | 0 (0.0%) |  |
| T3 | 11 (50.0%) | 7 (46.7%) |  |
| N stage |  |  | 1.000 |
| 0 | 20 (90.9%) | 13 (86.7%) |  |
| 1 | 2 (9.1%) | 2 (13.3%) |  |
| M stage |  |  | 1.000 |
| 0 | 19 (86.4%) | 13 (86.7%) |  |
| 1 | 3 (13.6%) | 2 (13.3%) |  |
| Nodal harvest, median (range) | 7.5 (5-12) | 6.0 (2.5-12.5) | 0.804 |
| 2010 WHO grade |  |  | 0.848 |
| G1 | 16 (72.7%) | 10 (66.7%) |  |
| G2 | 3 (13.6%) | 4 (26.7%) |  |
| G3 | 2 (9.1%) | 1 (6.7%) |  |
| Unknown | 1 (4.5%) | 0 (0%) |  |

ASA: American Society of Anesthesiologists; BMI: Body mass index; DGE: Delayed gastric emptying; ENETS: European Neuroendocrine Tumour Society; ISGPS: International Study Group on Pancreatic Surgery; ISGPF: International Study Group on Pancreatic Fistula; MIS: Minimally invasive surgery; POPF: Post-operative pancreatic ﬁstulae; PPPD: Pylorus-preserving pancreaticoduodenectomy; WHO: World Health Organization.

**Table 4 Factors associated with tumor recurrence after curative resection of nonfunctioning pancreatic neuroendocrine tumors**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Univariate analysis** | | | | **Multivariate analysis** | | |
| **HR** | **95%CI** | ***P* value** | **HR** | | **95%CI** | ***P* value** |
| Age > 60 yr | 0.40 | 0.09-1.83 | 0.239 |  | |  |  |
| Male | 1.95 | 0.62-6.16 | 0.254 |  | |  |  |
| Minimally invasive surgery | 0.61 | 0.18-2.09 | 0.432 | 1.062 | | 0.28-4.03 | 0.929 |
| Tumor size > 2.5 cm | 22.21 | 2.86-172.69 | 0.003 | 16.21 | | 1.99-128.8 | 0.009 |
| Positive resection margin | 1.52 | 0.33–6.99 | 0.589 |  | |  |  |
| Poor  differentiation, G3 | 71.55 | 6.43-795.75 | 0.001 | 24.429 | | 1.99-277.95 | 0.017 |
| Positive lymph node | 1.93 | 0.42–8.83 | 0.398 |  | |  |  |
| Lympho-vascular invasion | 8.77 | 2.75-27.93 | < 0.001 | 3.56 | | 0.96-13.2 | 0.058 |

HR: Hazard ratio.