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Retrospective Study

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

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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

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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[14,15,16]. 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 assited 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.

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