



Minimally invasive versus open surgery for nonfunctioning pancreatic neuroendocrine tumors: a systematic review and meta-analysis

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Introduction: Nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) have been diagnosed increasingly often but still represent rare pancreatic neoplasms. Surgery is a potentially curative approach for patients with NF-PNETs. In recent years, minimally invasive surgery (MIS) has been applied more frequently for surgical resection of NF-PNETs. The evidence for using MIS for NF-PNETs is still being determined and controversial.

Materials and Methods: PubMed, Cochrane Library, and the Web of Science database were searched systematically from its inception to July 2023. All studies comparing MIS versus open surgery (OPS) of NF-PNETs were included. The primary outcomes were the incidence of overall postoperative complications and pancreas-specific complications [postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE)]. The secondary measures were duration of operation, intraoperative blood loss, and length of postoperative hospital stay. Pooled results are presented as odds ratios (OR) or mean difference (MD) with a 95% CI.

Results: Five observational studies with a total of 1178 patients were included in the final analysis. The meta-analysis indicated that MIS attained less intraoperative blood loss (MD = -58.59, 95% CI [-92.76 to -24.41], $P < 0.01$) and shorter length of hospital stay (MD = -3.07, 95% CI [-5.28 to -0.87], $P < 0.01$) in contrast to open surgery for NF-PNETs. There were no significant differences concerning operative time (MD = 52.04, 95% CI [-8.74 to 112.81], $P = 0.67$), overall postoperative complications (OR = 0.78, 95% CI [0.59–1.03], $P = 0.08$), POPF (OR = 0.99, 95% CI [0.66–1.47], $P = 0.94$), and DGE (OR = 0.58, 95% CI [0.58–1.42], $P = 0.67$).

Conclusions: This study demonstrates that minimally invasive surgery for NF-PNETs is safe and associated with a considerably shorter postoperative hospital stay. Further studies are needed to verify the evidence.

Keywords: meta-analysis, minimally invasive surgery, nonfunctioning pancreatic neuroendocrine tumors

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:8250–8255

Received 3 August 2024; Accepted 22 October 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.ijw.com/international-journal-of-surgery.

Published online 22 November 2024

<http://dx.doi.org/10.1097/JS9.0000000000002143>

Introduction

Pancreatic neuroendocrine tumors (PNETs) are a rare and heterogeneous group of pancreatic neoplasms that are increasingly diagnosed.^[1] Consequently, most nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) only become symptomatic late and are often diagnosed at advanced stages, whereas some are discovered incidentally during imaging for other reasons.^[2,3] While in advanced stages, somatostatin analogs as well as everolimus are the most frequently used systemic therapies, surgery remains the cornerstone of curative treatment^[4,5].

Structured recommendations on the usage and exact indications of minimally invasive surgery (MIS) in NF-PNET surgery still need to be made. This meta-analysis aims to assess safety and efficacy of MIS for NF-PNETs compared to open pancreatic surgery.

Materials and methods

Three databases (PubMed, Cochrane Library, and Web of Science) were searched systematically from inception to July 2023. All studies comparing MIS versus OPS of NF-PNETs were included (Fig. 1). Primary outcomes included incidence of overall postoperative complications and pancreas-specific complications [postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE)]. The secondary measures were duration of

operation, intraoperative blood loss, and length of postoperative hospital stay. Pooled results are presented as odds ratios (OR) or mean difference (MD) with a 95% CI. The detailed information of search methods and has been displayed in the Supplementary Documents (Supplemental Digital Content 1, <http://links.lww.com/JS9/D566>) (Supplementary Table 4, Supplemental Digital Content 2, <http://links.lww.com/JS9/D567>).

Results

Postoperative complications

Postoperative complications were reported in four studies^[6–9] (Fig. 2A). Compared with the OPS group, the MIS group showed a trend towards lower overall complication rates, but this did not reach statistical significance (OR = 0.78, 95% CI [0.59–1.03], $P = 0.08$), neither for PD (OR = 1.10, 95% CI [0.43–2.79], $P = 0.84$) nor for DP (OR = 0.73, 95% CI [0.53–1.01], $P = 0.06$). Additionally, no significant difference was shown for severe complications (Clavien–Dindo > 3a) between the MIS and OPS groups (Fig. 2B).

Postoperative pancreatic fistula

All five studies reported the occurrence of POPF^[6–10] (Fig. 2C). The results indicate that there was no significant difference

HIGHLIGHTS

- Minimally invasive pancreatic application is popularly performed gradually while the advantages and disadvantages of minimally invasive pancreatic application are still debated.
- As for nonfunctioning pancreatic neuroendocrine tumors, the minimally invasive operation is not clear with robust evidence.
- The study combines the bibliometric review and systematic review to generate the current level of evidence for minimally invasive resection in treatment with nonfunctioning pancreatic neuroendocrine tumors first.

between MIS and OPS in the occurrence of POPF in patients with NF-PNETs (OR = 0.99, 95% CI [0.66–1.47], $P = 0.94$) and that there was no significant difference in the occurrence of POPF between PD and DP, respectively.

Delayed gastric emptying

Only one study reported postoperative DGE^[7] in patients with NF-PNETs without showing any significant advantage for MIS in

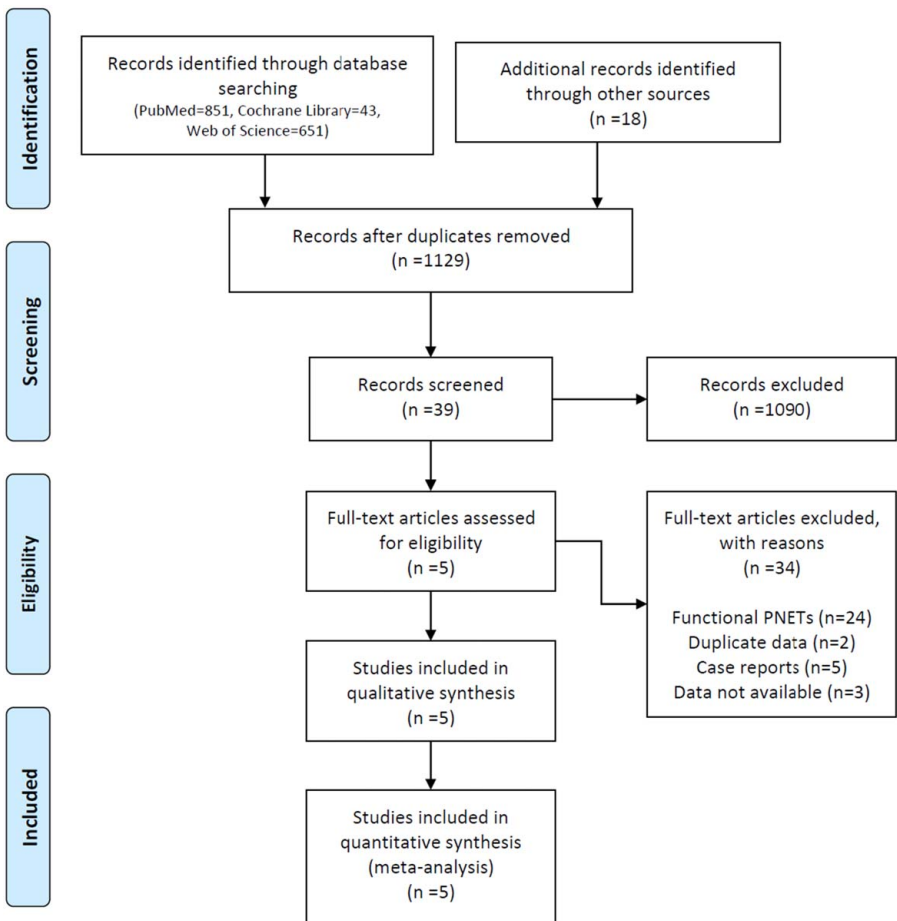


Figure 1. Literature screening process.

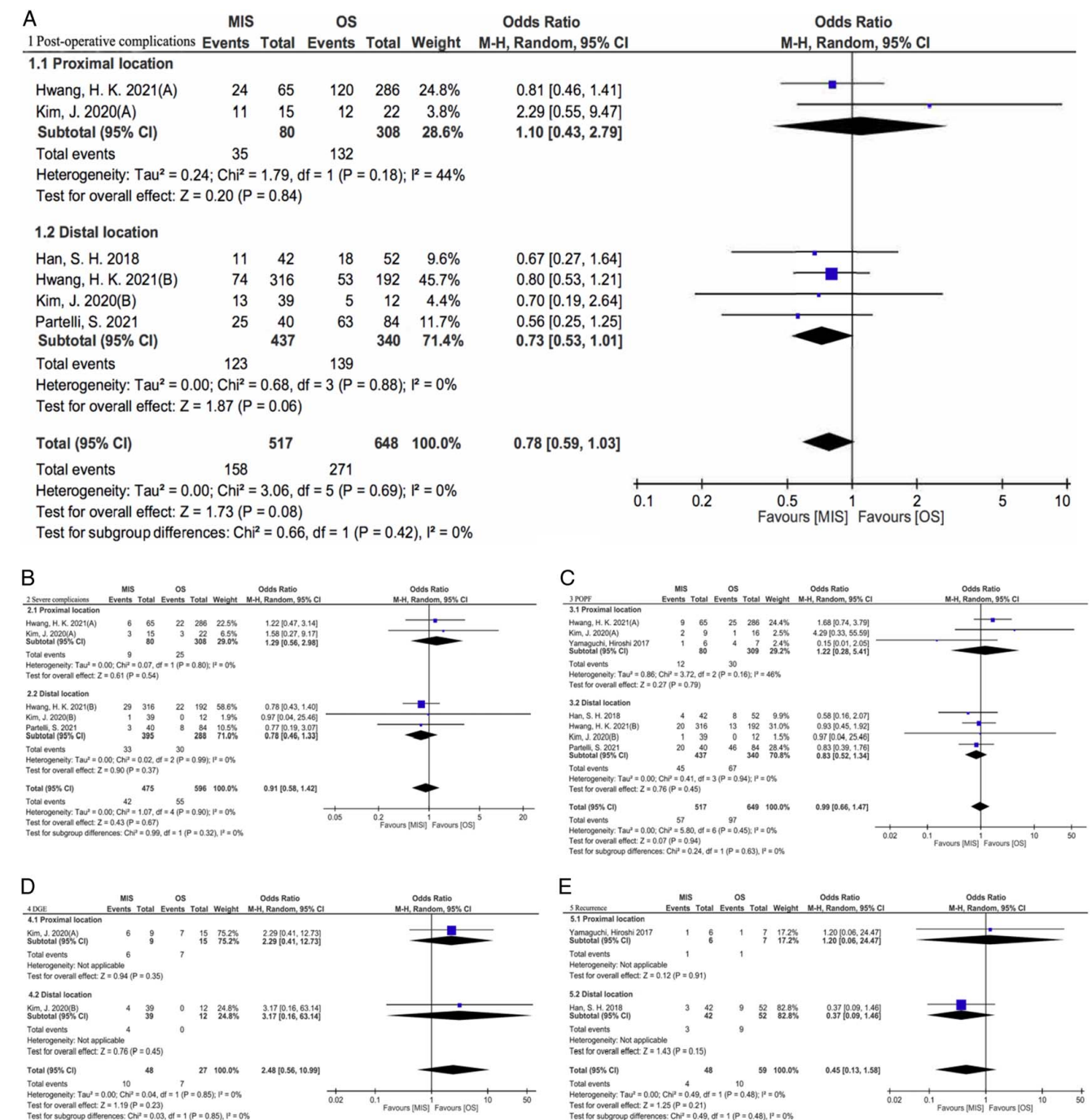


Figure 2. Meta-analysis results of dichotomous data. (A) Postoperative complications; (B) Severe complications; (C) POPF; (D) DGE; (E) Recurrence. DGE, delayed gastric emptying; POPF, postoperative pancreatic fistula.

the occurrence of DGE in either group analysis or integrated analysis showed ($OR = 0.58$, 95% CI [0.58–1.42], $P = 0.67$) (Fig. 2D).

Operation time

Three studies reported operative time^[6–8], and overall pooled analyses found that MIS did not significantly prolong the duration of surgery for patients with NF-PNETs ($MD = 52.04$, 95% CI [–8.74 to 112.81], $P = 0.67$) (Fig. 3A). However, the combined

results of two of those three studies showed that MIS significantly extended the duration of surgery for patients with PD ($MD = 118.07$, 95% CI [36.19–199.95], $P < 0.01$). In contrast, there was no significant difference between MIS and OPS for DP ($MD = 6.79$, 95% CI [–23.85 to 37.43], $P = 0.66$).

Intraoperative blood loss

Three studies included intraoperative blood loss^[6–8] as an outcome parameter, and meta-analysis results showed that MIS

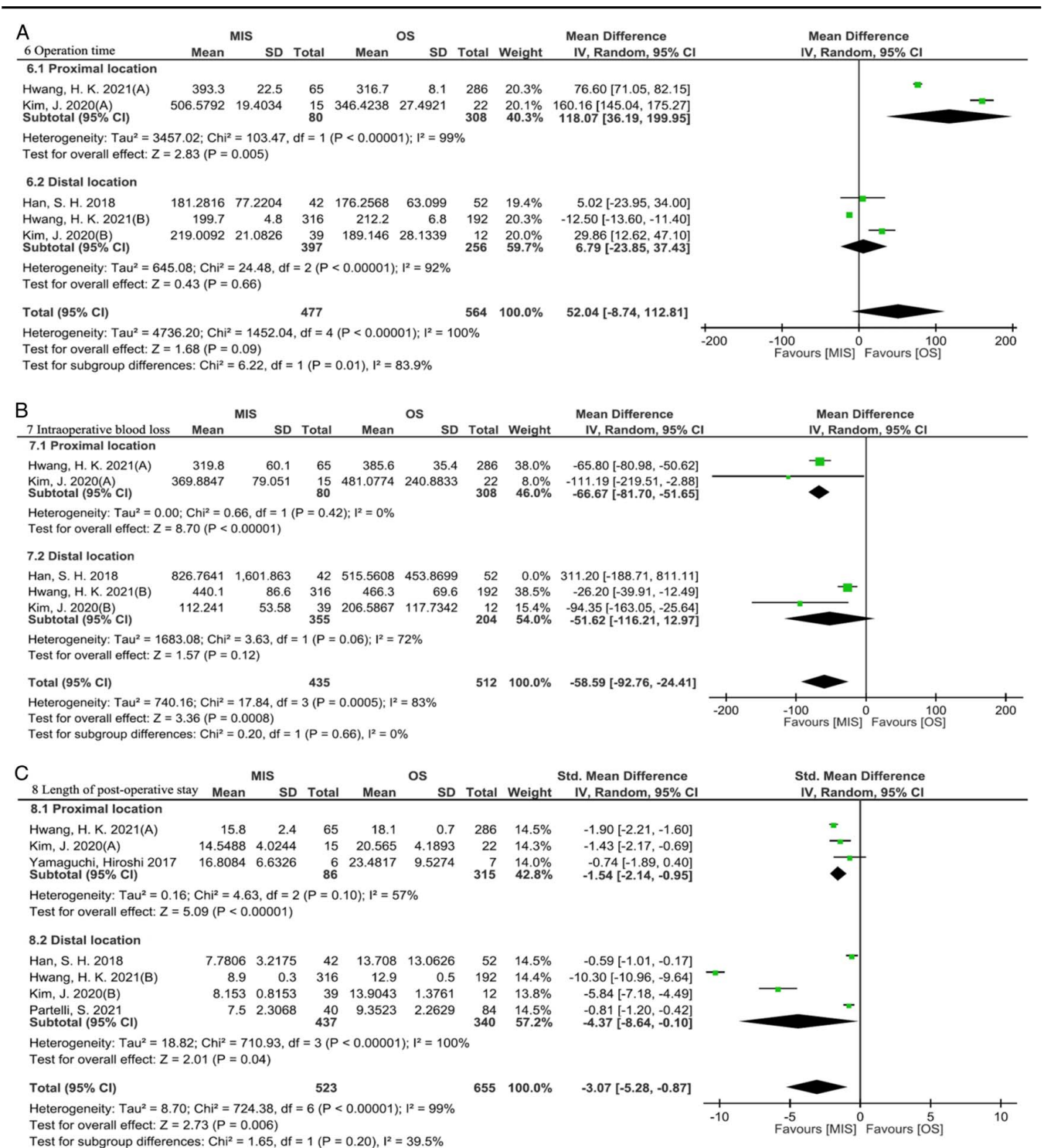


Figure 3. Meta-analysis results of dichotomous data. (A) Operation time; (B) intraoperative blood loss; (C) length of postoperative stay.

could effectively reduce intraoperative blood loss (MD = -58.59, 95% CI [-92.76 to -24.41], $P < 0.01$) (Fig. 3B). Subgroup analysis showed that MIS significantly reduced intraoperative blood loss in PD (MD = -66.67, 95% CI [-81.70 to -51.65], $P < 0.01$), while there was no significant difference between MIS and OPS in DP (MD = -51.62, 95% CI [-116.21 to 12.97], $P = 0.12$).

Length of postoperative stay

All studies assessed the length of postoperative hospital stay^[6-10] and the pooled analysis showed that MIS significantly reduced the length of hospital stay compared to OPS (MD = -3.07, 95% CI [-5.28 to -0.87], $P < 0.01$) (Fig. 3C). This difference was confirmed for both, PD (MD = -1.54, 95% CI [-2.14 to -0.95],

$P < 0.01$) and DP (MD = -4.37, 95% CI [-8.64 to -0.10], $P = 0.04$).

Other related postoperative outcomes

Supplementary Table 2 (Supplemental Digital Content 2, <http://links.lww.com/JS9/D567>) shows other postoperative outcomes of NF-PNET patients reported in a single study. It did not show apparent benefits for patients for MIS compared to OPS in PPH, intra-abdominal abscess, reoperation rates, or readmission. The basic information of included studies and assessment of included studies and quality of evidence has been demonstrated in Supplementary Documents (Supplemental Digital Content 1, <http://links.lww.com/JS9/D566>) (Supplementary Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/JS9/D567>, supplementary Table 1, Table 3, Table 5, Supplemental Digital Content 2, <http://links.lww.com/JS9/D567>).

Discussion

According to the results of this study, MIS is comparable to OPS for the treatment of NF-PNETs with potential benefits for patients regarding intraoperative blood loss and shorter length of hospital stay. From this analysis, MIS can be considered a safe surgical approach in selected patients with NF-PNETs.

While the MIS-associated reduction in blood loss (-60 ml) is of limited clinical impact, the 3-day reduction of hospital stay can be considered a significant advantage. Notably, the effects on postoperative hospital stay exist for both proximal and distal resection in NF-PNET patients, reflecting this as a general advantage. Independent of the surgical extent of the operation itself, minimal access may explain this fact. Considering postoperative complications in terms of POPF and DGE, as well as operative time, there were no significant differences between the MIS and the OPS groups. This was not influenced by the type of resection (partial PD vs. DP). In other words, MIS is safe and feasible compared to OPS, with similar rates of severe and overall postoperative complications suggesting that MIS can be a valuable alternative for surgical resection for NF-PNETs. The oncological – especially long-term – advantages or disadvantages of MIS have yet to be proven in the literature compared to OPS for PNET. However, this is prone to bias, and few randomized studies have addressed this as the primary outcome. From all the included studies in the present systematic review, overall survival and R0 resection rates were not sufficiently available for a statistically sound analysis.

Unavoidably, there are limitations in this study: 1. All included studies were nonrandomized and had low to moderate quality according to ROBINS-I evaluation. 2. Although subgroup analysis of proximal and distal locations was performed to minimize interstudy heterogeneity, we still could not obtain specific outcomes data caused by differences due to various surgical procedures, resulting in inevitable heterogeneity in some pooled outcomes. The level of evidence was not robust enough to provide solid recommendations for clinical practice.

Conclusion

Compared to OPS, MIS is possibly safe and feasible for treating NF-PNETs in experienced hands and selected patients

could benefit from a shorter hospital stay. However, well-designed studies are needed to confirm the advantages and disadvantages of MIS for NF-PNETs, especially with regard to robotic surgery.

Ethical approval

This is systematic review and meta-analysis which do not needs the ethical approval.

Consent

This is systematic review and meta-analysis which do not needs the ethical approval.

Source of funding

None.

Author contribution

W.K.Y., Z.Q.Y., and H.T.: study concept or design; W.K.Y., Z.Q.Y., and C.L.Y.: data collection; W.K.Y., Z.Q.Y., C.L.Y., and T.J.H.: data analysis or interpretation; W.K.Y. and H.T.: writing the paper; L.W., N.A., U.F.G., F.N., W.Z., and H.T.: critical review.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

This is systematic review and meta-analysis which do not needs the ethical approval. The study protocol is publicly available on PROSPERO (CRD42021259734). <https://www.crd.york.ac.uk/prospero/#recordDetails>.

Guarantor

Thilo Hackert.

Data availability statement

The study is a systematic review and meta-analysis and the data is extracted from public database.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Presentation

None.

Assistance with the study

None.

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