https://doi.org/10.1016/j.hpb.2023.02.014

REVIEW ARTICLE

Minimally-invasive versus open pancreatic enucleation: systematic review and metanalysis of short-term outcomes

Raffaello Roesel[1,1], Lorenzo Bernardi[2,1], Marco A. Bonino[1], Sotirios G. Popeskou[2], Fabio Garofalo[2] & Alessandra Cristaudi[2]

[1]Department of Visceral Surgery, University Hospital of Geneva (HUG), Rue Gabrielle-Perret Gentil 4, Geneve, and [2]Department of Visceral Surgery, Hospital of Lugano (EOC), Via Tesserete 46, 6900 Lugano, Switzerland

Abstract

Background: Minimally Invasive Pancreatic Enucleation, either laparoscopic or robot-assisted, is rarely performed. The aim of this study was to offer the current available evidence about the outcomes of minimally invasive pancreatic enucleations and explore the possible advantage of this approach over traditional surgery.

Methods: PubMed (MEDLINE), Cochrane Library and Embase (ELSEVIER) medical databases were searched for articles published from January 1990 to March 2022. Studies which included more than 10 cases of minimally-invasive pancreatic enucleation were included. Data on the outcomes were synthetized and meta-analyzed when appropriate.

Results: Twenty studies published between 2009 and 2022 with a total of 552 patients were included in the systematic review: three hundred fifty-one patients (63.5%) had a laparoscopic intervention, two hundred and one (36.5%) robot-assisted with a cumulative incidence of conversion rate of 5%.

Minimally-invasive surgery was performed in 63% of cases on the body/tail of the Pancreas and in 37% of the cases on the head/uncinate process of the Pancreas. The cumulative post-operative 30 days - mortality rate was 0.2% and the major postoperative morbidity (Clavien-Dindo III-IV-V) 35%. Clinically relevant pancreatic fistula was observed in 17% of the patients.

Compared with the standardized open approach (n: 366 patients), mean length of hospital stay was significantly reduced in patients undergoing minimally invasive pancreatic enucleation (2.45 days, $p = 0.003$) with a favorable trend for post-operative major morbidity (Clavien-Dindo III-IV) (- 24% RR, p: 0.13). Operative time, blood loss and clinically relevant pancreatic fistula rate were comparable between the two groups. One hundred and fourteen robot-assisted enucleations entered in a subgroup analysis with comparable results to open surgery.

Conclusion: Minimally-Invasive approach for pancreatic enucleation is safe, feasible and offers short-term clinical outcomes comparable with open surgery. The potential benefit of robotic surgery will need to be verified in further studies.

Received 13 May 2022; accepted 20 February 2023

Correspondence

Raffaello Roesel, Department of Visceral Surgery, Geneva University Hospital Rue Gabrielle-Perret-Gentil 4 1205 Geneva, Switzerland. E-mail: raffaello.roesel@gmail.com

[1] *Raffaello Roesel and Lorenzo Bernardi equally contributed to this work.*

Introduction

Pancreatic Enucleation is a valid surgical option for benign or low-grade malignant lesions to achieve both radical resection and organ-function sparing.[1] Moreover, recent literature reported that enucleation, when appropriate, may be associated with reduced perioperative morbidity in comparison with standard resection.[2,3] Pancreatic enucleation is a challenging operation whose main difficulties lie in proper intra-operative identification of the resection margins and precise dissection of the parenchyma avoiding weakening/injuries of the main pancreatic duct. The reported rate of post-operative pancreatic fistula is not irrelevant, ranging around 30–40%.[4,5] A minimally invasive approach is apparently well suited for pancreatic enucleation given the small surgical sample or the lack of reconstructive procedures and could therefore favorably impact on post-operative recovery. However, whether or not the minimally invasive approach is advantageous in pancreatic enucleation is still not supported by a consistent body of evidence.

The aim of this systematic review and metanalysis is firstly to investigate the available evidence on the surgical outcomes of minimally invasive pancreatic enucleation (MI-pEn) and secondly to explore the possible advantages of this approach over conventional open enucleation (O-pEn).

Methods

This study was performed in accordance with the guidelines of preferred reporting items for systematic reviews and metanalysis (PRISMA) 2015.[6]

Literature search strategy and study identification

A systematic literature search of Pubmed (MEDLINE), Cochrane Library and Embase (ELSEVIER) databases was performed independently by two researchers (RR and MAB, 22nd march 2022). The following combination of terms was used for the research ("Pancreas"OR"Pancreatic")AND("Enucleat*"). We restricted our research on papers published from January 1990 to March 2022.

Eligibility criteria

The reference list was screened to find relevant articles that mentioned MI-pEn (laparoscopic or robot-assisted pancreatic enucleation) in the abstracts. Either prospective or retrospective studies were considered eligible. No language restriction was applied. Data from conference proceedings and reviews were excluded. Full text reading of the articles screened was then implemented to include in the analysis only papers that reported data on surgical outcomes specifically for the MI-pEn group with a number of patients treated greater or equal to 10. The case load limit of 10 patients treated was adopted to reduce the risk of "learning curve" bias for a rare and high technically demanding surgery.

Data collection and outcome measure

Title and abstract were evaluated for every study screened in the literature to assess the eligibility by two different reviewers (RR and LB). The articles not adherent to the topic or inappropriate for the study design were excluded. Full texts of the potentially eligible studies were evaluated to assess their inclusion in the analysis. Any disagreement was resolved by discussion. For the studies that met the eligibility criteria title, authors, journal, years, country, study period, study design, number of patients, patient characteristics, indication for surgery, type of surgery, post-operative outcomes and complications were extracted.

Our primary endpoint was Length of Stay (LoS). Secondary endpoints were operative time, blood-loss, rate of major post-operative morbidity (Clavien-Dindo III-IV-V) and clinically-relevant pancreatic fistula (**CRPF**) rate.

According to the definition of clinically relevant pancreatic fistula, which is defined as a drainage output of any measurable volume of fluid with a level of amylase greater than 3 times the upper level of normal institutional serum amylase, associated with a clinically significant development/condition directly related to POPF; we considered CRPF: ISGPF 2005 Pancreatic Fistula B/C[7] and ISGPF 2016 Pancreatic Fistula B/C[8] as some studied were published before 2016.

Quality assessment

Two researchers (RR, LB) independently assessed for methodological quality and risk of bias among the included studies according to ROBINS-I tool for non-randomised studies and Cochrane risk tool for randomized trials[9] (Table 1).

Statistical analysis

All analyses were performed according to the original treatment allocation (intention-to-treat analysis). Descriptive statistics were performed and data was expressed as mean (SD) or median (range) where appropriate. For binary outcome data, the relative risks (RR) and 95% confidence intervals (CIs) were estimated using the Mantel-Haenszel method. For continuous outcome data, the mean differences (MD) and 95% CIs were estimated using inverse variance weighting; when means and/or standard deviations (SDs) were not reported, they were estimated from the reported medians, ranges, and sample size as described by Hozo et al.[10] A fixed-effects model was used in all meta-analyses, and the same analyses were redone in a random-effects model. Heterogeneity was assessed using the Higgins I^2 test, I^2 values > 50% indicated the presence of significative heterogeneity.[11]

Potential sources of heterogeneity were explored using different sensitivity analyses: comparing fixed-effects versus random-effects models (thus incorporating heterogeneity using the second method), checking the results of cumulative (sequentially including studies by date of publication) and influence meta-analyses (calculating pooled estimates by omitting one study at a time).

Table 1 MI p-En: patients characteristics and short-term outcomes

Reference	Country	Year	Period	N MI-pEn	Lap/Rob	Age (Years)	M/F	Tumour Diagnosis
Luo et al.[12]	China	2009	2000–2007	14	14/0	NA	NA	NEN: 14
Dedieu A. et al.[13]	France	2010	1999–2007	23	23/0	49 ± 16[b]	12/11	NEN:15, MCN:1, IPMN:1, Others:6
Fernàndez-Cruz et al.[14]	Spain	2012	1999–2007	13	13/0	61 ± 32.4[a]	NA	NEN: 13
Zureikat AH. et al.[15]	USA	2013	2008–2012	10	0/10	NA	NA	NA
Choi K. et al.[16]	Korea	2014	2005–2011	11	11/0	43 ± 12.5[b]	1/10	MCN:4, SCN:4, Others:3
Song K. et al.[17]	Korea	2015	2005–2013	30	30/0	51.2 ± 11.8[b]	NA	NA
Jin J. et al.[18]	China	2016	2010–2015	31	0/31	51 ± 17.8[a]	11/20	NEN:13, SCN:4, IPMN:8, Others:6
Tian F. et al.[20]	China	2016	2000–2015	60	0/60	45.2 ± 13.1[b]	21/39	NEN: 60
Shi Y. et al.[19]	China	2016	2010–2014	26	0/26	50.1 ± 14.1[b]	11/16	NA
Zhang. R. et al.[21]	China	2016	2001–2014	15	15/0	49.5 ± 13.1[b]	6/9	NEN:6, MCN:2, SCN:1, others:6
Dokmak S. et al.[41]	France	2016	2008–2015	30	30/0	50 ± 14[b]	20/10	NEN:19, MCN:6, Others:6
Siech M. et al.[23]	Germany	2017	2008–2016	48	48/0	NA	NA	NA
Belfiori G. et al.[24]	Italy	2018	2003–2016	15	12/3	46.6 ± 43.3[a]	8/7	NEN: 15
Di Benedetto et al.[25]	Italy	2018	2013–2018	12	0/12	51.9 ± 43.6[a]	6/6	NEN: 12
Chen K. et al.[26]	China	2018	2004–2018	30	30/0	49.6 ± 13.6[b]	8/22	NEN:13, MCN:4, SCN:4, Others:9
Ore A. S. et al.[27]	USA	2019	2014–2016	43	31/12	54.6 ± 15.3[a]	30/13	NEN:33, MCN:4, Others:6
Najafi N. et al.[28]	Germany	2020	2008–2015	19	7/12	50 ± 45.6[a]	9/10	NEN: 17, IPMN: 1, Others:1
Shigenori Ei et al.[29]	Germany	2021	2001–2020	40	21/19	55.3 ± 16.1[a]	13/27	NEN:11, MCN:6, SCN:5, IPMN:12, Others:6
Bencini L. et al.[30]	Italy	2021	2014–2020	16	0/16	55.6 ± 40.1[a]	10/6	NEN: 14, Others:2
Jianwei Xu et al.[31]	China	2021	2014–2020	66	66/0	43.6 ± 16.7[b]	21/45	NEN:34, MCN:4, SCN:4, Others:24

Ref.	Combined Surgery n. (%)	Tumor Site H–U/B-T	TS (mm)[a]	Conver. n. (%)	OT (min)	BL (ml)	Mort. n. (%)	Morb. n. (%)	PF B/C n. (%)	Re-Op n. (%)	Hosp. (days)
12	0 (0)	5/9	NA	2 (13)	NA	NA	0 (0)	NA	NA	0 (0)	NA
13	0 (0)	8/15	24.5 ± 18[b]	2 (8.7)	124 ± 80[b]	64 ± 162[b]	1 (4.3)	4 (17)	1 (4.3)	1 (4.3)	9 ± 3[b]
14	13 (100)	NA	28.6 ± 1.6[a]	0 (0)	166 ± 157[a]	213 ± 150[a]	0 (0)	NA	3 (23)	0 (0)	6.3 ± 0.8[a]
15	NA	NA	NA	0 (0)	206 ± 67[b]	NA	0 (0)	5 (50)	3 (30)	0 (0)	6.6 ± 7.7[a]
16	0 (0)	0/11	40 ± 3.3[b]	0 (0)	97.4 ± 16.6[b]	36 ± 11.9[b]	0 (0)	1 (9)	1 (9)	0 (0)	5.5 ± 1.7[b]
17	NA	3/27	21 ± 16[b]	0 (0)	191 ± 45.3[b]	NA	0 (0)	3 (10.7)	3 (10.7)	0 (0)	7.8 ± 3.5[b]
18	NA	16/15	20.3 ± 1.8[a]	0 (0)	100 ± 7.5[a]	30 ± 31[a]	0 (0)	NA	12 (38.7)	0 (0)	13 ± 3.5[a]
20	0 (0)	27/33	13.7 ± 3.4[a]	3 (5)	117 ± 66.5[a]	35 ± 247.5[a]	0 (0)	8 (13)	6 (10)	0 (0)	12 ± 7.5[a]
19	0 (0)	11/16	23.3 ± 12[b]	0 (0)	124.6 ± 50.9[b]	76 ± 85.4[b]	0 (0)	12 (46.2)	7 (27)	0 (0)	22.6 ± 15.6[b]
21	0 (0)	3/12	34 ± 18[b]	1(6.7)	118.2 ± 33.1[b]	80 ± 71.2[b]	0 (0)	6 (40)	3 (20)	0 (0)	7.9 ± 3.4[b]
41	NA	NA	NA	1 (3)	107 ± 61[b]	63 ± 142[b]	0 (0)	11 (37)	5 (15)	0 (0)	12 ± 9[b]
23	NA	NA	NA	5 (12)	NA	NA	0 (0)	23 (47)	NA	5 (12)	27 ± 48[a]
24	NA	4/11	15.8 ± 14[a]	3 (20)	150 ± 54.9[a]	NA	0 (0)	10 (66.7)	3 (20)	1 (6.7)	19.3 ± 15.3[a]
25	NA	5/7	9.6 ± 10[a]	0 (0)	214 ± 151[a]	56 ± 75[a]	0 (0)	4 (33.3)	1 (8.3)	0 (0)	3.6 ± 2.5[a]
26	NA	NA	NA	0 (0)	135 ± 148[b]	118 ± 186[b]	0 (0)	5 (16.7)	2 (6.7)	0 (0)	12.6 ± 19.4[b]
27	0 (0)	NA	NA	7 (16.3)	136 ± 18.75[a]	NA	NA	12 (28)	7 (16.7)	1 (2.3)	4 ± 0.5[a]
28	0 (0)	1/18	27.3 ± 44[a]	0 (0)	197 ± 176[a]	68 ± 116[a]	0 (0)	5 (26.3)	5 (26.3)	0 (0)	12.3 ± 13.6[a]
29	NA	8/32	23 ± 4.5[a]	1 (2.5)	125 ± 17.3[a]	50 ± 22.5[a]	0 (0)	7 (18%)	7 (18)	2 (5)	7.5 ± 1[a]
30	2 (12.5)	NA	26.6 ± 20[a]	NA	187 ± 183[a]	NA	0 (0)	2 (12.5)	2 (12.5)	NA	12.3 ± 13.6[a]
31	NA	42/24	37.6 ± 56[b]	3 (4.5)	198 ± 261[b]	702 ± 1512[b]	0 (0)	16 (24.2)	13 (19.7)	NA	17.6 ± 27.2[b]

Legend: **N**: Number, **M/F**: Male/Female, **TS**: Tumor Size, **MPD**: Tumor-Main Pancreatic Duct distance. **NA**: Not Assessed, **NEN**: Neuroendocrine Neoplasm, **MCN**: Mucinous Neoplasm, **SCN**: Serous Neoplasm, **IPMN**: Intraductal Papillary Mucinous Neoplasm. **Ref**: reference, **H–U/B-T**: Head-Uncinate process/Body-Tail, **TS:** Tumor Size, **Conv**: Conversion (number),**OT**: Operative Time, **BL**: Blood Loss, **Mort**: Mortality, **Morb**: Morbidity **PF**: Pancreatic Fistula, **Re-Op**: Re-Operation, **Hosp**: Hospitalization, **NA**: Not Assessed.
[a] Mean ± SD calculated with Hozo formulas.
[b] Mean ± SD from the original article.

Publication bias was assessed by generating a funnel plot and performing a linear regression test for funnel plot asymmetry.[12] All analyses were conducted using the R 3.3.1 package meta (see Fig. 1).

Results

Literature search

The literature search on PubMed (MEDLINE), Cochrane Library and Embase (ELSEVIER) medical databases revealed Two thousand three-hundreds eighty-three articles. Two thousand three-hundreds twenty-two articles were excluded as they were duplicates or did not match the main topic. Sixty-one articles were evaluated in full text. Forty-one articles were excluded as they were review/expert-opinion, case series of less than 10 patients or did not report relevant outcomes object of the analysis. Twenty articles were included in the systematic review. Twelve articles were then excluded from the metanalysis since they did not report a direct comparison between open and minimally-invasive pancreatic enucleations (Fig. 1).

Systematic review – qualitative analysis

Twenty studies[13–32] published between 2009 and 2022 with a total of 552 patients undergoing MI-pEn: were included in the systematic review (Table 1A-B). Three hundred fifty-one patients (63.5%) had a laparoscopic intervention, two hundred and one (36.5%) robot-assisted. The median number of patients reported in each paper was 24.5 (IQR: 14.8–33.3), the largest cohort (n:66) is published by a Chinese group in a recent paper.[32] The mean age was 50.4 ± 4.5 years with prevalence of male patients (77.7%). The pathology was recorded in 16 articles for 439 enucleations with neuroendocrine neoplasm (NEN) being the most common diagnosis (n: 289, 67%), followed by mucinous cystic neoplasm (MCN) (n: 31, 7%), intraductal papillary mucinous neoplasm

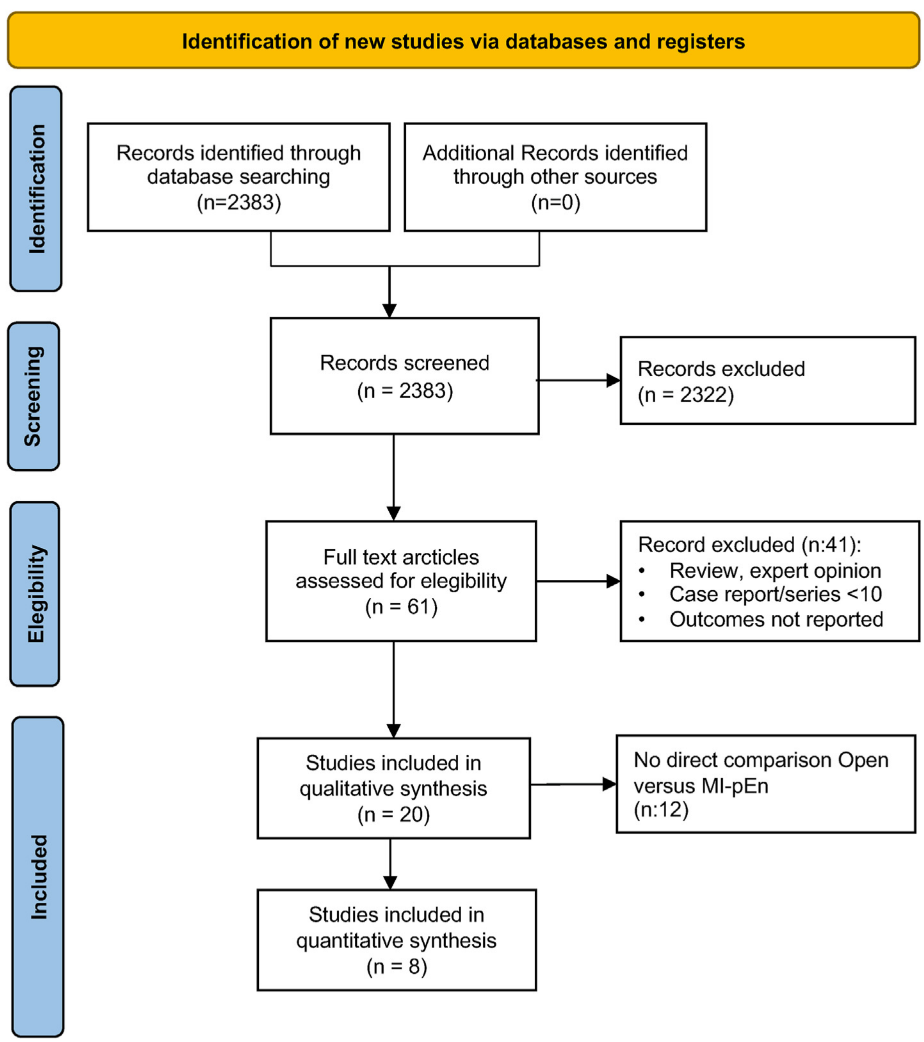

Figure 1 Identification of new studies via databases and registers

Table 2 ROBINS-I tool (Stage II) for assessing risk of bias in non-randomised studies

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Bias in selection of reported result
Song K. et al.[17]	High Risk	High Risk	Low Risk	No Information	Low Risk	Low Risk	Low Risk
Jin J. et al.[18]	High Risk	High Risk	Low Risk	No Information	Low Risk	Low Risk	Low Risk
Tian F. et al.[20]	Moderate Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Shi Y. et al.[19]	High Risk	High Risk	Low Risk	No Information	High Risk	High Risk	High Risk
Zhang. R. et al.[21]	High Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Belfiori G. et al.[24]	High Risk	High Risk	Low Risk	No Information	Low Risk	Low Risk	Low Risk
Ore A. S. et al.[27]	High Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Shigenori Ei et al.[29]	Moderate Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

(IPMN) (n: 22, 5%) and serous cystic neoplasm (SCN) (n: 22, 5%). Others rare indication as symptomatic pseudocyst, solid pseudopapillary tumor and Lymphangioma occurred in 74 cases (17%). Thirteen articles reported the location of 363 lesions: 133 (37%) were located in the head/uncinate process whereas 230 (63%) in the body/tail of the Pancreas; in the robot-assisted enucleation subgroup[19–21,26,31] 55 (43.6%) *versus* 71 (56.4%). The mean tumor size was 24.6 ± 8.7 mm (n: 377, 14 studies). The mean operative time was 149 ± 39 min (n: 490, 18 studies); the mean intra-operative blood loss ranged was 122 ± 180 cc (n: 376, 13 studies). Cumulative conversion rate to open surgery was 5% (28/552, 20 studies). One patient is reported to die the post-operative period (30 days mortality), giving a mean mortality rate of 0.2%. Major post-operative morbidity (Clavien-Dindo III-IV-V) was recorded in 134 of 381 patients (35.1%). Clinically relevant pancreatic fistula was reported in 84 of 490 patients (17.1%). Re-Operation was required in 10 of 470 patients (2.1%). The mean length of hospital stay was 11.5 ± 6.3 days (n: 490, 19 studies).

Metanalysis of comparative studies

MI-pEn versus O-pEn

Eight studies[18–22,25,28,30] with a total of 626 patients were included in the metanalysis[18–22,25,28,30]: 366 patients treated with standard open enucleation and 260 treated either with laparoscopy of robot-assisted enucleation. All included studies were comparatively retrospective and thoroughly described the study design and methods (Tables 3 and 4). All of them compared minimally-invasive to open surgery in pancreatic enucleation with a case load of more than 10 patients treated with MI-pEN. Three studies reported only robot-assisted cases for the minimally invasive arm,[19–21] and two others[18,22] only laparoscopic cases.

Pooled Analysis (Table 4) showed that MI-pEn and O-pEn group were comparable in terms of operation time (MD: - 14.63 min; 95% CI, −40.81/11.56; $p = 0.27$; $I^2 = 85\%$) but with a significative reduction of blood loss in the minimal invasive group (MD: - 89.12 mL; 95% CI, −124.27/-53.98; $p < 0.01$; $I^2 = 0\%$) (Fig. 2A and B).

Regarding the postoperative outcomes, both major morbidity (RR: 0.74; 95% CI: 0.49/1.10; p = 0,13; $I^2 = 0\%$) and CRPF (RR: 0.90; 95% CI: 0.63/1.28; $p = 0.55$; $I^2 = 21\%$) did not reach a statistical significance difference between the two groups (Fig. 2C and D). Instead, the Length of Stay was significantly reduced in the MI-pEn group as compared with O-pEn (MD: −2.45 days; 95% CI: −3.96/-0.95; $p = 0.003$; $I^2 = 57\%$) (Fig. 2E).

Not all outcomes of interest in the meta-analysis are reported in all comparative studies included in the meta-analysis. Specifically, operative time is defined in all studies; Blood-loss, major morbidity, POPF, and Length of stay are based on a number of studies with a total number of patients included in the meta-analysis of respectively: 4/8 (320), 7/8 (561), 7/8 (via 561) and 7/8 (583).

Robot-assisted pEn versus O-pEn

Three retrospective comparative studies with a total of 219 patients were included in the metanalysis.[19–21] Only 3/117 cases of conversion to open surgery were reported. Operation time, post-operative major morbidity as clinically relevant POPF and Length of stay did not differ between the two groups but remains significative the reduction of blood loss in the Robot-assisted compared to the open procedure (MD: - 81.26 mL; 95% CI: −143.35/-19.18; $p < 0.01$; $I^2 = 0\%$) although only two studies analyzed this outcome (Table 4).

No further subgroup analysis was performed according to indication for surgery or MI-approach as separate subgroup (ex. Laparoscopic versus robotic surgery); data were not provided or sufficient for a measure effect estimation.

Quality assessment and risk of bias

Critical appraisal of the included studies revealed heterogeneous quality. With regard to internal validity, no clinical study was blinded or randomized. Three studies performed and analysed more than 40 enucleations. According to the ROBINS-I risk of bias in non-randomized studies[33] the overall risk of bias assessment for the studies included resulted "High" (Table 2).

In our analyses, "I" value (heterogeneity) was 57% for the primary endpoint. "I" values of the secondary endpoints were

Table 3 Characteristics of the studies included in the Metanalysis

Reference	Inclusion Criteria:	Exclusion Criteria:	Study Aim:	Study Design:	Tumor Diagn. N:	Qual. Assessment:
Song K. et al.[17]	• Benign or low-grade malignant tumors of the pancreas who underwent pancreatic enucleation.	NA	Evaluate the postoperative clinical outcomes after pancreatic enucleation	Retrospective	NEN:24, MCN:9, SCN:9, IPMN:7	Poor
Jin J. et al.[18]	• Enucleation for benign or borderline tumor of the Pancreas.	NA	Evaluate post-operative benefit of robotic pancreatic enucleation versus open	Retrospective (Prospective Database)	NEN:26, MCN:4, SCN:6, IPMN:12	Poor
Tian F. et al.[20]	• pNET max. diameter 2 cm • Distance between tumour and main pancreatic duct greater than 2 mm • No evidence of pancreatic duct dilatation.	• Multiple pNETs or ectopic lesions • History of pancreatic resection • Procedures synchronous with enucleation • Distant metastasis • Pancreatitis • Pancreatic Adenocarcinoma • Severe cardiac or pulmonary disease	Assess the safety and efficiency of robotic surgery for the enucleation of small pNETs	Retrospective (Prospective Database) Propensity score Matching.	NEN: 120	Fair
Shi Y. et al.[19]	•Generally good condition • Absence of multiple tumours • At least 1–2 mm away from the main pancreatic duct • No evidence of malignancy • No previous history of upper abdominal surgery.	NA	Discuss the clinical evaluation and postoperative complications after robotic pancreatic enucleation and compare it with open surgery	Retrospective.	NA	Poor
Zhang. R. et al.[21]	•Pancreatic Enucleation	• Enucleations with combined organ resection.	Compare perioperative outcomes of patients undergoing Laparoscopic Enucleation and Open Enucleation and to assess the pancreatic function after Laparoscopic Enucleation	Retrospective. (Prospective Database) Intention-to-treat analysis.	NEN:17, MCN:5, SCN:4	Poor
Belfiori G. et al.[24]	• Enucleations for sporadic insulinoma	NA	Compare short-term and long-term outcomes of minimally invasive laparoscopic or robotic enucleation (MIC-EN) and open enucleation (O-EN) for	Retrospective (Prospective Database)	NEN: 71	Poor

Table 3 (*continued*)

Reference	Inclusion Criteria:	Exclusion Criteria:	Study Aim:	Study Design:	Tumor Diagn. N:	Qual. Assessment:
			sporadic benign insulinoma			
Ore A. S. et al.[27]	• Pancreatic Enucleation	• Patients when the surgical approach was not specified • Concomitant surgical procedures performed	Verify that minimally-invasive (MI) pancreatic enucleation is associated with decreased composite major morbidity (CMM) compared to open	Retrospective (Prospective Database). Intention-to-treat analysis.	NEN:89, MCN:7, SCN:1	Poor
Shigenori Ei et al.[29]	• Enucleation for benign tumors of the Pancreas	• Tumors with main pancreatic duct (MPD) involvement • Suspected preoperative evidence of malignancy	Compare outcomes between Minimally Invasive Enucleation (ME) and open enucleation (OE)	Retrospective (Prospective Database). Intention-to-treat analysis. Propensity score Matching.	NEN:36, MCN:13, SCN:18, IPMN:42	Fair

Legend: **Diagn**: Diagnosis, **Qual**: Quality, **NEN**: Neuro-Endocrine Neoplasia, **MCN**: Mucinous Cistyc neoplasia, **SCN**: Sierous Cistyc Neoplasia, **IPMN**: Intraductal Papillary Mucinous Neoplasm.

0 and 21% for rate of major post-operative morbidity and clinically-relevant pancreatic fistula respectively; 85 and 0% for Operative Time and Blood Loss respectively. Linear regression test of funnel plot asymmetry did not highlight any anomalies so that we considered the occurrence of publication bias unlikely. Cumulative and influence analysis did not find any change of the significatively of the results for all the outcomes analyzed.

Discussion

Pancreatic enucleation has emerged in the last years as a valuable option for the treatment of pancreatic benign or low-grade neoplasia[1,34–37] avoiding endocrine and exocrine sequelae of standard pancreatic resections.[1] With the advancement of laparoscopic and robotic techniques, minimally invasive approach

Table 4 Characteristics of the patients included in the Meta-Analysis

Ref.	Groups	N	Tumor Site H–U/B-T	Tumor Size, mm	OT, min	Blood Loss, ml	Morbidity C-D > II, n (%)	POPF B/C, n (%)	LOS, days
17	Open (En) Lap (En)	35 30	24/11 3/27	31 ± 19[b] 21 ± 16[b]	169,8 ± 47[b] 191 ± 45.3[b]	NA	NA	NA	11.9 ± 6.2[b] 7.8 ± 3.5[b]
18	Open (En) Rob (En)	25 31	19/6 16/15	23.75 ± 3.75[a] 20 ± 2.75[a]	149.5 ± 20[a] 100 ± 7.5[a]	NA	4 (16) 2 (6.5)	13 (52) 12 (38.7)	20.75 ± 4.25[a] 13 ± 3.5[a]
20	Open (En) Rob (En)	60 60	30/30 27/33	13,8 ± 3,6[a] 13,7 ± 3,4[a]	150 ± 50[a] 117 ± 66.5[a]	80 ± 295[a] 35 ± 247.5[a]	6 (10) 2 (3)	10 (17) 6 (10)	13.5 ± 20.25[a] 12 ± 7.5[a]
19	Open (En) Rob (En)	17 26	9/8 11/16	35 ± 19[b] 23 ± 12[b]	198.5 ± 70.7[b] 124.6 ± 50.9[b]	157.1 ± 114.2[b] 76 ± 85.4[b]	1 (5.8) 1 (3.8)	3 (17.6) 7 (26.9)	23.9 ± 16.8[b] 22.6 ± 15.6[b]
21	Open (En) Lap (En)	22 15	15/7 6/9	33 ± 27[b] 34 ± 18[b]	155,2 ± 44.3[b] 118.2 ± 33.1[b]	195.5 ± 103,4[b] 80 ± 71.2[b]	1 (4.5) 2 (13.3)	3 (13.6) 3 (20)	11.2 ± 5.7[b] 7.9 ± 3.4[b]
24	Open (En) Lap + Rob (En)	56 15	37/22 4/11	NA	180 ± 71.25[a] 150 ± 54.92[a]	NA	13 (23,2) 2(13.3)	12 (21.4) 3 (20)	9 ± 10.5[a] 19.25 ± 15.33[a]
27	Open (En) Lap + Rob (En)	71 43	NA	NA	125 ± 9.83[a] 136 ± 18.75[a]	NA	24 (34) 12 (28)	14 (19.7) 7 (16.3)	5 ± 0.33[a] 4 ± 0.5[a]
29	Open (En) Lap + Rob (En)	80 40	23/56 8/31	22 ± 2.5[a] 23 ± 4.25[a]	125 ± 10.83[a] 125 ± 17.25[a]	100 ± 41.67 50 ± 22.5	16 (20) 7(18)	17 (21) 7 (18)	8 ± 1.13[a] 7.5 ± 1[a]

Legend: **Ref**: reference, **Lap** Laparoscopic, **Rob**: Robotic, **H–U/B-T**: Head-Uncinate Process/Body-Tail, **OT**: Operative Time, **C-D > II**: Clavien-Dindo Morbidity III-IV-V, **POPF B/C**: Clinically relevant Post-Operative Pancreatic Fistula, grade B/C sec ISGPS 2016, **RO**: Re-Operation, **LOS**: Length of Stay.

[a] Mean and SD calculated with Hozo formulas.

[b] Mean and SD from the original article.

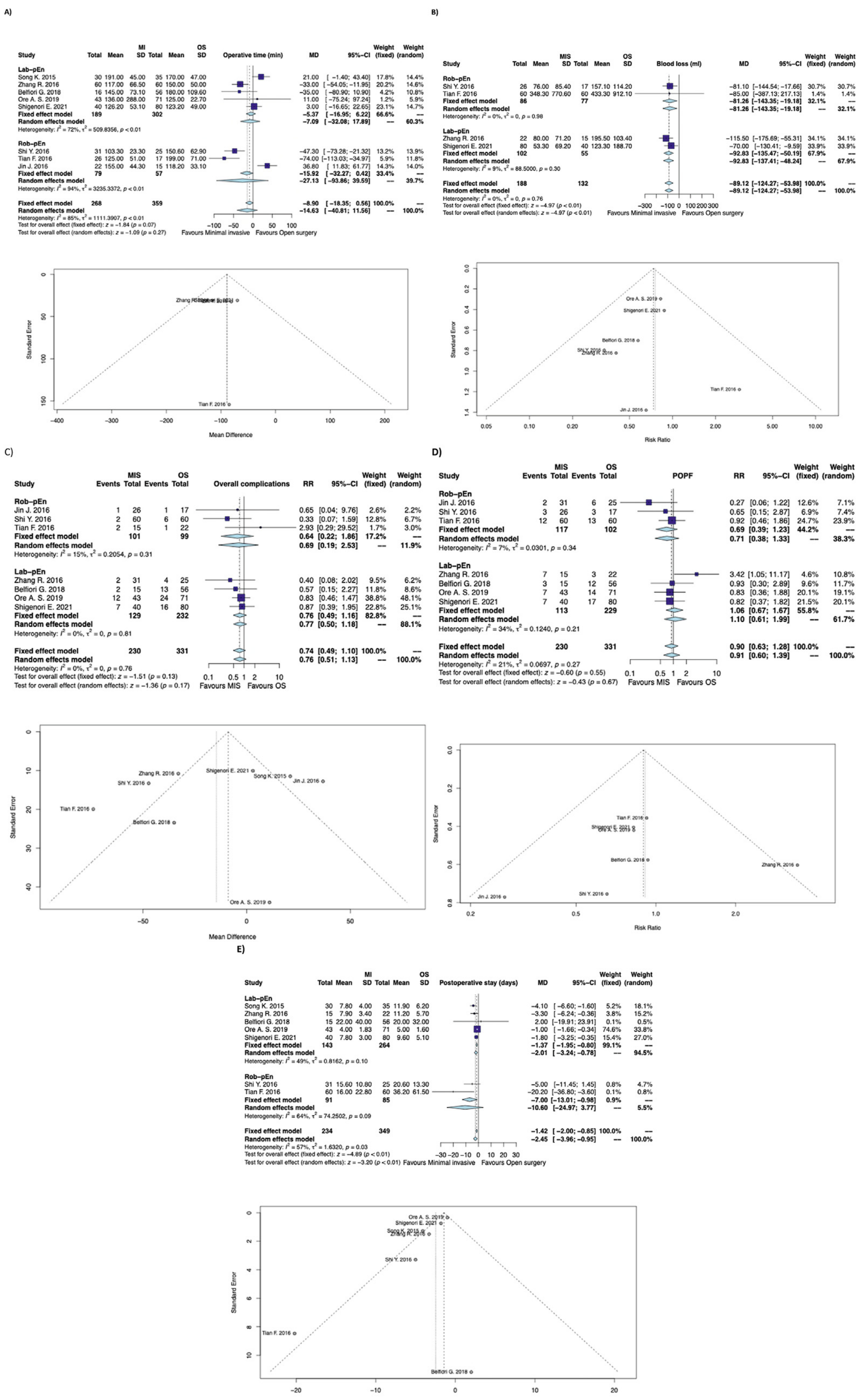

Figure 2 Forest and Funnel Plot of the main outcomes.Legend: **A**: Operative Time, **B**: Blood Loss, **C**: Major Morbidity (Clavien-Dindo III-IV), **D**: POPF B/C, **E**: Length of Stay

for pancreatic lesions is used more often given its advantages in terms of cosmetics and early recovery.[38,39] Although MI-pEn has been reported as feasible and safe in experienced high-volume centers,[13,14,17] the wide-spread implementation of this approach in the real world is strongly limited by lack of specific recommendations. No randomized trial is nowadays available and evidence is therefore limited to retrospective series. The only meta-analysis published in literature by Guerra et al.[40] in 2018, suggested a advantage of the minimally invasive approach with a significantly shorter length of hospital stay (mean difference: 5.18 days $P < 0.0001$) but questionable in light of the small sample size considered (166 MI p-En patients) and relatively low quality of the studies included with 3/8 reporting less than 10 minimally-invasive procedures and therefore potentially biased by confounders that was reflected into the elevate heterogeneity reported on the primary outcome ($I^2 = 61\%$). A review in the light of the controversial data recently published (after 2017) to validate this result and revive the indication for minimally invasive surgery of pancreatic enucleation seems therefore appropriate. In particular Ore et al., in 2019[25] published a retrospective cohort study of 114 pancreatic enucleation (43 minimally-invasive) implementing a multivariate analysis that failed to find an association between surgical approach and operating time or post-operative morbidity but highlighted an advantage in term of length of hospital stay for the MI-pEn patients (5 *vs* 4 days, $p < 0.05$).

Shigenori Ei et al. from Heidelberg in 2021[30] made a comparison between open and minimally invasive approach after a propensity (2:1) score matching for tumor location, histopathology, age, BMI, and sex. The post-match comparison regarded 120 patients. They found a statistically significant difference in term of intra-operative blood loss (100 cc vs 50 cc) in favor of minimally-invasive surgery but no difference in terms of hospital stay. The results of the meta-analysis are based on all eight studies only in the case of operative time; the other outcomes are based on seven studies except for blood loss, the result of which stems from 4 studies with about half the predicted 320/627 patients. In the latter case although significance is itself secondary to sample size, the inability to extend the analysis to all studies included a priori in the meta-analysis is a critical issue.

Our work collects the broad number of pancreatic enucleations specifically attempted with minimally invasive approach (n: 552). Our updated cumulative analysis suggests that minimally-invasive pancreatic enucleation is a safe and feasible procedure with only 5% conversion rate but affected by a non negligeable complication rate with 35% of major morbidity and 17% of clinically relevant fistula. However, morbidity in MI-pEn appears be comparable to standard open pancreatic enucleation[1,41] and therefore probably associated with the type of procedure (pancreatic enucleation) rather than the approach (minimally-invasive or open) adopted. Those relatively high morbidity rate in any case do not translate into elevated mortality rate (0.2%). The results of this cumulative analysis are comparable to another systematic review conducted on the topic by Dalla Valle et. in 2018.[42]

The metanalysis observe that a minimally invasive approach for pancreatic enucleation achieves short-term clinical outcomes comparable with the standard open approach. The possible advantage in terms of reduction in the length of hospitalization (−2.45 days; $p = 0.003$) and post-operative major morbidity (Clavien-Dindo III-IV) (- 24%, p: 0.13) must be considered in light of the limitations expressed below.

In our metanalyis the selection bias cannot be ruled out, owing to the lack of randomization and the scarcity of baseline data in some of the included studies. For most studies it is unclear whether the patients included in the open enucleation group would also have been suitable for minimally-invasive enucleation. Moreover, the approach is generally reported as dependent to the preference of the attending surgeon without debating important factors that may have influenced this decision. Superficial or deep parenchyma localization as distance from the main pancreatic duct were seldom reported and neoplasms enucleated by laparoscopy were more likely located in the distal pancreas (63%) in comparison to the head/uncus (37%).[13,14,17–22,25,26,29,30,32,43–46] Given that tumor location is thought to affect the risk of developing a clinically relevant pancreatic fistula because of the risk of pancreatic ducts injury,[5,47] this selection bias has to be taken into account. Another Risk factor that should be considered is the cystic morphology of the lesion, associated to significantly increased morbidity in pancreatic enucleation.[48] However, apart from two papers that did not mention the specific relative frequency,[18,20] cystic lesions were reported in similar frequency between patients undergoing minimally-invasive (55/204, 26.9%) and open approach (86/314: 27.4%) in our comparative studies. One of the other important points that was not possible to investigate was whether MI-PEn was associated with more R1 resections, because none of the studies reported this parameter. Attention to this point should be encouraged in further publications, also in view of recent controversies about its clinical relevance in NEN.[49] From a technical point of view neither pre-operative pancreatic stent placement,[50] nor Intra-Operative Ultrasound (IOUS) was routinely adopted in the papers analyzed.

Notwithstanding the low evidence of the studies included, our work condenses the best available evidence and confirms the findings of most individual recent papers.[28–30,46] To reinforce the implementation of a minimally invasive approach for pancreatic enucleation a multicenter RCT specifically evaluating the short-term outcomes, would be of considerable relevance. This, however, appears difficult to implement in light of the rarity of the surgical indication in question, the technical difficulty of the procedure (learning curve bias) and surgeon preferences. Properly designed studies with direct comparison to laparoscopy are also needed to better assess the additional value of Robotics.

Authors contributions

Conception and design of the work: RR, LB, AC.Acquisition of data: RR, LB.Data analysis: RR, MAB.Data interpretation: RR, MAB, FG, AC.Drafting the article: RR, MAB, FG, AC.Critical revision of the article and final approval of the version to be published: all authors.

Ethics approval

No ethical approval was required.

Informed consent

Informed consent does not apply.

Conflict of interest

The authors declare no competing interests.

References

1. Zhou Y, Zhao M, Wu L, Ye F, Si X. (2016) Short- and long-term outcomes after enucleation of pancreatic tumors: an evidence-based assessment. *Pancreatology* 16:1092–1098.
2. Beane JD, Borrebach JD, Billderback A, Onuma AE, Adam MA, Zureikat AH *et al*. (2021) Small pancreatic neuroendocrine tumors: Resect or enucleate? *Am J Surg* 222:29–34.
3. Gratian L, Pura J, Dinan M, Roman S, Reed S, Sosa JA. (2014) Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. *Ann Surg Oncol* 21:3515–3521.
4. Faitot F, Gaujoux S, Barbier L, Novaes M, Dokmak S, Aussilhou B *et al*. (2015) Reappraisal of pancreatic enucleations: a single-center experience of 126 procedures. *Surgery* 158:201–210.
5. Heeger K, Falconi M, Partelli S, Waldmann J, Crippa S, Fendrich V *et al*. (2014) Increased rate of clinically relevant pancreatic fistula after deep enucleation of small pancreatic tumors. *Langenbeck's Arch Surg* 399: 315–321.
6. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M *et al*. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 350: g7647.
7. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
8. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591.
9. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD *et al*. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.
10. Hozo SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5:13.
11. Higgins JP. (2003) Measuring inconsistency in meta-analyses. *BMJ*, 327.
12. Egger Mathias GDS, Martin Schneider, Christoph Minder. (1997) Bias in meta-analysis detected by simple, graphical test. *BMJ*, 515.
13. Luo Y, Liu R, Hu MG, Mu YM, An LC, Huang ZQ. (2009) Laparoscopic surgery for pancreatic insulinomas: a single-institution experience of 29 cases. *J Gastrointest Surg* 13:945–950.
14. Dedieu A, Rault A, Collet D, Masson B, Sa Cunha A. (2011) Laparoscopic enucleation of pancreatic neoplasm. *Surg Endosc* 25:572–576.
15. Fernandez-Cruz L, Molina V, Vallejos R, Jimenez Chavarria E, Lopez-Boado MA, Ferrer J. (2012) Outcome after laparoscopic enucleation for non-functional neuroendocrine pancreatic tumours. *HPB* 14:171–176.
16. Zureikat AH, Moser AJ, Boone BA, Bartlett DL, Zenati M, Zeh HJ, 3rd. (2013) 250 robotic pancreatic resections: safety and feasibility. *Ann Surg* 258:554–559.
17. Choi KS, Chung JC, Kim HC. (2014) Feasibility and outcomes of laparoscopic enucleation for pancreatic neoplasms. *Ann Surg Treat Res* 87: 285–289.
18. Song KB, Kim SC, Hwang DW, Lee JH, Lee DJ, Lee JW *et al*. (2015) Enucleation for benign or low-grade malignant lesions of the pancreas: single-center experience with 65 consecutive patients. *Surgery* 158: 1203–1210.
19. Jin JB, Qin K, Li H, Wu ZC, Zhan Q, Deng XX *et al*. (2016) Robotic enucleation for benign or borderline tumours of the pancreas: a retrospective analysis and comparison from a high-volume Centre in Asia. *World J Surg* 40:3009–3020.
20. Shi Y, Peng C, Shen B, Deng X, Jin J, Wu Z *et al*. (2016) Pancreatic enucleation using the da Vinci robotic surgical system: a report of 26 cases. *Int J Med Robot* 12:751–757.
21. Tian F, Hong XF, Wu WM, Han XL, Wang MY, Cong L *et al*. (2016) Propensity score-matched analysis of robotic versus open surgical enucleation for small pancreatic neuroendocrine tumours. *Br J Surg* 103:1358–1364.
22. Zhang RC, Zhou YC, Mou YP, Huang CJ, Jin WW, Yan JF *et al*. (2016) Laparoscopic versus open enucleation for pancreatic neoplasms: clinical outcomes and pancreatic function analysis. *Surg Endosc* 30:2657–2665.
23. Dokmak S, Fteriche FS, Aussilhou B, Levy P, Ruszniewski P, Cros J *et al*. (2017) The largest European single-center experience: 300 laparoscopic pancreatic resections. *J Am Coll Surg* 225:226–234 e2.
24. Siech M, Strauss P, Huschitt S, Bartsch DK, Wittel U, Keck T. (2017) The indications for laparoscopic pancreatectomy. *Dtsch Arztebl Int* 114: 263–268.
25. Belfiori G, Wiese D, Partelli S, Wachter S, Maurer E, Crippa S *et al*. (2018) Minimally invasive versus open treatment for benign Sporadic insulinoma comparison of short-term and long-term outcomes. *World J Surg* 42:3223–3230.
26. Di Benedetto F. (2018) *Ultrasound-guided robotic enucleation of pancreatic neuroendocrine tumors*. Surgical Innovation.
27. Chen K, Pan Y, Mou YP, Wang GY, Zhang RC, Yan JF *et al*. (2019) Evolution of laparoscopic pancreatic resections for pancreatic and periampullary Diseases: perioperative outcomes of 605 patients at a high-volume center. *J Laparoendosc Adv Surg Tech* 29:1085–1092.
28. Ore AS, Klompmaker S, Stackhouse K, Solis-Velasco M, Francken M, Callery MP *et al*. (2019) Does surgical approach affect outcomes of enucleation for benign and low-grade pancreatic tumors? An ACS-NSQIP evaluation. *HPB* 21:1585–1591.

29. Najafi N, Mintziras I, Wiese D, Albers MB, Maurer E, Bartsch DK. (2020) A retrospective comparison of robotic versus laparoscopic distal resection and enucleation for potentially benign pancreatic neoplasms. *Surg Today* 50:872–880.
30. Ei S, Mihaljevic AL, Kulu Y, Kaiser J, Hinz U, Buchler MW *et al*. (2021) Enucleation for benign or borderline tumors of the pancreas: comparing open and minimally invasive surgery. *HPB* 23:921–926.
31. Lapo Bencini IU, Trafeli Martina, Paolini Claudia, Moraldi Luca, Tribuzi Angela, Pacciani Sabrina *et al*. (2021) Robotic pancreatic surgery: minimally invasive approach to challenging operations. *Minerva Surgery* 76:138–145.
32. Xu J, Li F, Zhan H, Liu H, Wu D, Hu S *et al*. (2021) Laparoscopic enucleation of pancreatic tumours: a single-institution experience of 66 cases. *ANZ J Surg* 91:106–110.
33. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M *et al*. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355:i4919.
34. Tsuchikawa T, Tanaka K, Nakanishi Y, Asano T, Noji T, Nakamura T *et al*. (2021) Clinical impact of organ-preserving surgery for pancreatic neuroendocrine neoplasms: a single-center experience. *Pancreas* 50: 196–200.
35. Heidsma CM, Tsilimigras DI, van Dieren S, Rocha F, Abbott DE, Fields R *et al*. (2021) Indications and outcomes of enucleation versus formal pancreatectomy for pancreatic neuroendocrine tumors. *HPB* 23:413–421.
36. Wang P, Wei J, Wu J, Xu W, Chen Q, Gao W *et al*. (2018) Diagnosis and treatment of solid-pseudopapillary tumors of the pancreas: a single institution experience with 97 cases. *Pancreatology* 18:415–419.
37. Kaiser J, Fritz S, Klauss M, Bergmann F, Hinz U, Strobel O *et al*. (2017) Enucleation: a treatment alternative for branch duct intraductal papillary mucinous neoplasms. *Surgery* 161:602–610.
38. Riviere D, Gurusamy KS, Kooby DA, Vollmer CM, Besselink MG, Davidson BR *et al*. (2016) Laparoscopic versus open distal pancreatectomy for pancreatic cancer. *Cochrane Database Syst Rev* 4Cd011391.
39. Asbun HJ, Stauffer JA. (2012) Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. *J Am Coll Surg* 215: 810–819.
40. Guerra F, Giuliani G, Bencini L, Bianchi PP, Coratti A. (2018) Minimally invasive versus open pancreatic enucleation. Systematic review and meta-analysis of surgical outcomes. *J Surg Oncol* 117:1509–1516.
41. Huttner FJ, Koessler-Ebs J, Hackert T, Ulrich A, Buchler MW, Diener MK. (2015) Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms. *Br J Surg* 102: 1026–1036.
42. Dalla Valle R, Cremaschi E, Lamecchi L, Guerini F, Rosso E, Iaria M. (2019) Open and minimally invasive pancreatic neoplasms enucleation: a systematic review. *Surg Endosc* 33:3192–3199.
43. Dokmak S, Aussilhou B, Fteriche FS, Belghiti J, Sauvanet A. (2017) Hanging Maneuver for Stomach traction in laparoscopic distal pancreatic resections: an original technique Applied in 218 patients. *Dig Surg* 34:89–94.
44. Jilesen AP, van Eijck CH, Busch OR, van Gulik TM, Gouma DJ, van Dijkum EJ. (2016) Postoperative outcomes of enucleation and standard resections in patients with a pancreatic neuroendocrine tumor. *World J Surg* 40:715–728.
45. Giuliani T, De Pastena M, Paiella S, Marchegiani G, Landoni L, Festini M *et al*. (2021) Pancreatic Enucleation Patients Share the Same Quality of Life as the General Population at Long-Term Follow-Up: A Propensity-Score Matched Analysis. *Ann Surg*. https://doi.org/10.1097/SLA.0000000000004911. Epub 2021/04/16.
46. Kabir T, Tan ZZX, Syn N, Chung AYF, Ooi L, Goh BKP. (2019) Minimally-invasive versus open enucleation for pancreatic tumours: a propensity-score adjusted analysis. *Ann Hepatobiliary Pancreat Surg* 23: 258–264.
47. Duconseil P, Marchese U, Ewald J, Giovannini M, Mokart D, Delpero JR *et al*. (2018) A pancreatic zone at higher risk of fistula after enucleation. *World J Surg Oncol* 16:177.
48. Wang X, Tan CL, Zhang H, Chen YH, Yang M, Ke NW *et al*. (2018) Short-term outcomes and risk factors for pancreatic fistula after pancreatic enucleation: a single-center experience of 142 patients. *J Surg Oncol* 117:182–190.
49. Marchegiani G, Landoni L, Andrianello S, Masini G, Cingarlini S, D'Onofrio M *et al*. (2019) Patterns of recurrence after resection for pancreatic neuroendocrine tumors: who, when, and where? *Neuroendocrinology* 108:161–171.
50. Giuliani T, Marchegiani G, Girgis MD, Crino SF, Muthusamy VR, Bernardoni L *et al*. (2020) Endoscopic placement of pancreatic stent for "Deep" pancreatic enucleations operative technique and preliminary experience at two high-volume centers. *Surg Endosc* 34: 2796–2802.