Review Article

Pancreatic head cancer: Open or minimally invasive pancreaticoduodenectomy?

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Abstract

Pancreatic head cancer still represents an insurmountable barrier for patients and pancreatic surgeons. Pancreaticoduodenectomy (PD) continues to be the operative standard of care and potentially curative procedure for pancreatic head cancer. Despite the rapid development of minimally invasive techniques, whether the efficacy of minimally invasive pancreaticoduodenectomy (MIPD) is noninferior or superior to open pancreaticoduodenectomy (OPD) remains unclear. In this review, we summarized the history of OPD and MIPD and the latest staging and classification information for pancreatic head cancer as well as the proposed recommendations for MIPD indications for patients with pancreatic head cancer. By reviewing the MIPD- *vs*. OPD-related literature, we found that MIPD shows noninferiority or superiority to OPD in terms of safety, feasibility, enhanced recovery after surgery (ERAS) and several short-term and long-term outcomes. In addition, we analyzed and summarized the different MIPD outcomes in the USA, Europe and China. Certain debates over MIPD have continued, however, selection bias, the large number of low-volume centers, the steep MIPD learning curve, high conversion rate and administration of neoadjuvant therapy may limit the application of MIPD for pancreatic head cancer.

Keywords: Feasibility; minimally invasive pancreaticoduodenectomy; open pancreaticoduodenectomy; pancreatic head cancer; safety

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Introduction

Pancreatic cancer is a highly lethal human disease with a 5-year overall survival rate of 8% (1,2). This malignancy is the fourth and sixth leading cause of cancer-related deaths in the USA and China, respectively (2,3). Based on tumor location, pancreatic cancer is divided into two types — pancreatic head cancer and pancreatic cancer of the body and tail. The incidence of the former is evidently higher than that of the latter. Pancreatic head cancer accounts for 60%–70% of pancreatic adenocarcinomas, whereas 20%–25% of pancreatic cancers arise in the body and tail of the pancreas and 10%–20% of pancreatic cancers diffusely involve the pancreas (4). Meanwhile, the resectable rate of pancreatic cancer of the body is also higher than that of the tail. In this review, we will focus on the surgical choice for pancreatic head cancer. Radical surgery is regarded as one of the most important therapeutic approaches for pancreatic head cancer. Pancreaticoduodenectomy (PD, Whipple procedure) is

always adopted as the standard surgery for pancreatic head cancer. With the rapid development of minimally invasive techniques and the widespread application of minimally invasive concepts in the various fields of surgery, more surgeons prefer minimally invasive pancreaticoduodenectomy (MIPD) to open pancreaticoduodenectomy (OPD). MIPD includes the following procedures: laparoscopic pancreaticoduodenectomy (LPD), robotic pancreaticoduodenectomy (RPD), hybrid laparoscopic and robotic pancreaticoduodenectomy (HLRPD), and laparoscopic-assisted pancreaticoduodenectomy (LAPD).

History of PD

History of OPD

PD was initially described in 1898 by an Italian surgeon. Whipple and Parson carried out and reported the first successful surgical resection based on the pioneers' experience in 1935, when the technique began to be widely known worldwide. In 1940, Whipple performed the first successful one-stage radical PD (5). Subsequently, Child indicated that the anastomosis order should be pancreaticojejunostomy, cholecystenterostomy/choledochoenterostomy, and gastrojejunostomy in 1944. The modern Whipple procedure (OPD) took shape from then on. During the development of OPD, many surgeons have tried many other surgical procedures, including pylorus-preserving pancreaticoduodenectomy (PPPD), extended pancreaticoduodenectomy (EPD), regional pancreatectomy (RP), and total pancreatectomy (TP). However, it is still controversial whether PPPD will influence the short-term (R0 resection) and long-term (overall survival) oncological outcomes of patients with pancreatic head cancer. Otherwise, EPD, RP and TP will result in increased morbidity and mortality and shortened overall survival time. Therefore, the classic Whipple procedure (OPD) is still regarded as the standard surgical procedure for patients with pancreatic head cancer.

History of MIPD

The developmental history of MIPD can be divided into two periods — the start-up phase (1990s) and rapid development phase (after the 2000s). The first MIPD was reported by Gagner and Pomp in 1994, and the surgical procedure was PPPD (6). Subsequently, they published 10 MIPD cases in 1997 and indicated that MIPD had no advantage over OPD. From then on, surgeons experienced 10 years of slow development with MIPD. After entering the 21st century, this complicated procedure, MIPD, became easy to learn and master due to the rapid development of laparoscopic instruments and the emergence of high definition lenses. In 2007, an Indian surgeon reported a large retrospective study of selected patients who underwent LPD, including 9 patients with pancreatic head cancer. A large number of LPD studies were reported in high-volume centers worldwide in the following years. The first RPD was initially published by Giulianotti in 2003. He performed RPD for 8 patients, including 3 patients with pancreatic head cancer (7). Notably, the application of RPD was restricted due to expensive instruments required.

OPD vs. MIPD

After a century of development, OPD has matured and may now be performed quite smoothly. Although it is still a complicated and highly risky operation, the postoperative morbidity has decreased gradually with the advancement of surgical techniques, the perioperative mortality has decreased to less than 5%, and the postoperative 5-year overall survival rate has increased to more than 20%. Compared with OPD, MIPD is still at an early stage, and many key issues remain to be solved. For example, the indications for MIPD are still controversial in different hospitals; the comparison data about safety, feasibility, short-term and oncological outcomes between MIPD and OPD are still unconvincing. Currently, high-volume hospitals throughout the world perform most of the MIPD procedures, and data on the short-term and long-term outcomes of MIPD originated from these large-scale institutions. In summary, MIPD is still in its infancy.

Staging and classification of pancreatic head cancer

The latest 8th edition of the American Joint Committee on Cancer (AJCC) staging manual has revised the TNM staging criteria for pancreatic cancer. The new staging system highlights the influence of tumor size and the number of positive lymph nodes on the prognosis of pancreatic cancer. According to this new system, stage T1 is subdivided into T1a, T1b and T1c based on tumor size; patients with smaller tumors have better outcomes. Extrapancreatic extension is removed from the definition of primary tumor, as it is difficult to determine.

Unresectability is removed from the definition of T4 because the T category is used to illustrate the extent of invasion and should not be subjective. Patients who have more than 3 positive lymph nodes are predicted to have a poor prognosis (8). A recent German study enrolled 256 pancreatic cancer patients who underwent curative resection to investigate the role of the new staging system in predicting the overall survival of patients with pancreatic cancer. Interestingly, the previous pT3 subgroup (according to the 7th edition of the staging system) was reclassified into four different pT stages in the new system, in which the percentage of pT2 was the highest (58.6%). In this subgroup, survival is significantly different between patients with pT1–pT2 tumors and those with pT3 tumors (9).

TNM staging has been regarded as one of the most important factors for determining whether OPD or MIPD is the best choice to manage pancreatic head cancer. Therefore, updates to the staging guidelines might change the indications for MIPD.

Resectability determines whether patients with pancreatic head cancer can undergo radical resection and the optimal time to perform surgery. According to the 2018 National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma, pancreatic head cancer can be classified into four categories: resectable, borderline resectable, locally advanced and disseminated. This classification system is mainly based on the pancreatic computed tomography (CT) protocol. However, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines indicate that both resectable and borderline resectable pancreatic cancer are part of the category of potentially curable pancreatic cancer, which is a new definition (10). Clinical guidelines are all supported by high-quality evidence. Some studies have indicated that some patients with locally advanced pancreatic head cancer can be recategorized as potentially curable after neoadjuvant therapy (11-13). Therefore, patients with resectable, borderline resectable and locally advanced pancreatic head cancers might be considered candidates to receive radical resection, namely, PD.

Recommendations for MIPD indications of pancreatic head cancer

For pancreatic head cancer, PD is accepted as the operative standard of care. According to the results of recent studies and our own experiences, we summarized the process of choosing the optimal surgical procedure for pancreatic head cancer (*Figure 1*). de Rooij *et al*. have discussed their opinion on indications and contraindications for MIPD (14). First, they noted the importance of study selection bias and the learning curve of MIPD. In their opinion, patients with tumor involvement of the major vessels (portomesenteric vein, or the superior mesenteric artery or vein), a history of chronic pancreatitis, history of neoadjuvant radiotherapy or morbid obesity should be excluded from undergoing MIPD. In addition, patients with a history of open upper abdominal surgery and those with large tumors and/or those with pT3/pT4 tumors should not undergo operations performed by surgeons who are at the early or middle stages of the MIPD learning curve (14).

Neoadjuvant chemoradiotherapy might induce local inflammation and increase the difficulty of performing minimally invasive surgery, but this possibility has not been supported by high-quality evidence. For relatively simple surgeries, such as distal pancreatectomy and gastrectomy, chemoradiotherapy would not lead to increased complexity for the surgeon. Moreover, if patients received neoadjuvant chemoradiotherapy before MIPD, it would increase the complexity of the surgery.

For patients with resectable pancreatic head cancer who have been treated with neoadjuvant chemoradiotherapy, OPD would be the best choice; if not, MIPD could be considered. For patients with borderline resectable and locally advanced pancreatic head cancer, neoadjuvant chemoradiotherapy should be used for tumor downstaging and an increase in resectability; thus, OPD should be the best choice for those patients. Selection of the most appropriate surgical procedure is also dependent on the learning curve phase of the surgeon. Only if the surgeon is in the late phase of the learning curve or is an expert in MIPD, should MIPD be the first choice for patients with pancreatic cancer.

MIPD *vs.* OPD in terms of safety, feasibility and outcomes

A large number of studies and meta-analyses have been carried out to compare the safety, feasibility, short-term and long-term outcomes between MIPD and OPD (6,15-23). Most studies have demonstrated that MIPD shows similar safety, feasibility and outcomes to OPD, including for operative time, major morbidity, and mortality. However, it has been reported that some factors are

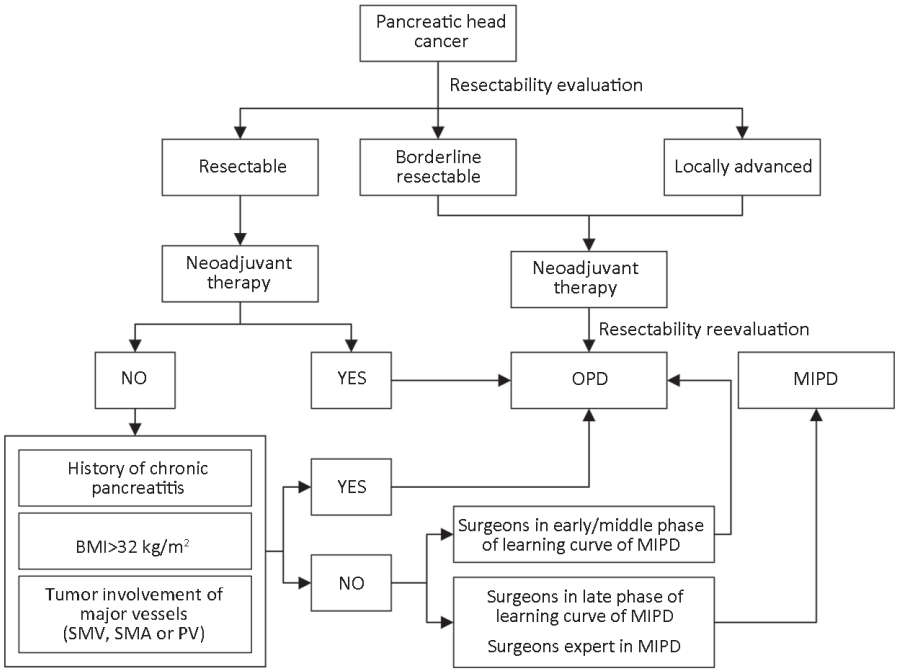

Figure 1 Recommendations of MIPD and OPD indications for pancreatic head cancer. The decision-aid flow chart was based on available evidence and related guidelines, experience of surgeons worldwide and our expertise. MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; BMI, body mass index; SMV, superior mesenteric vein; SMA, superior mesenteric artery; PV, portal vein.

associated with inferior outcomes. For example, when MIPD is performed by surgeons at the early phase of the learning curve or at low-volume centers (number of MIPD <10 or 20 cases per year), patients may experience a longer operative time, more blood loss, higher morbidity and mortality, and shorter survival time than OPD. The outcomes of MIPD might also differ because of socioeconomic factors or the differences in medical concepts between different regions or countries. In this part of the paper, we focus on the studies involving pancreatic head cancer (*Table 1*, *2*).

Safety, feasibility and short-term outcomes

With advancements in surgical techniques and minimally invasive devices, MIPD has become a relatively safe and feasible option for certain patients with pancreatic head cancer.

Although MIPD has an operative time that is comparable to OPD after the learning curve is completed, 7 studies (28,36-38,41,42,45) from high-volume centers reported that the operative time of MIPD was longer than that of OPD. A study from China concluded that the operative time of MIPD was longer than that of OPD if performed between 2010 and 2012; however, the difference was not statistically significant in 2013. This finding highlights the significance of the learning curve. In addition, 7 studies (24,25,32,33,35,39,40), whose data primarily came from the American National Cancer Database (NCDB), did not include data on the operative time. In addition, 5 studies (26,27,31,43,44) indicated that the difference in the operative time between OPD and MIPD was not statistically significant. Therefore, a consensus has been reached that only if MIPD is performed by an experienced surgeon from a high-volume center could the time not be prolonged compared with OPD.

MIPD is a safe procedure in terms of estimated blood loss (EBL). Although the differences in blood loss between OPD and MIPD were not included in 9 studies (24,25,27,32,33,35,39,40,44), all the blood loss of MIPD in each of 5 studies (28,36,37,41,42) was less than that of OPD. Notably, the results were unconvincing considering that the ASA classification of MIPD was lower than that of OPD and that the tumor size of patients undergoing MIPD was smaller than that of patients undergoing OPD in two respective studies. Meanwhile, 5 studies showed no statistical significance between OPD and MIPD for EBL.

Table 1 MIPD *vs.* OPD for pancreatic head cancer: safety, feasibility and outcomes (2017–2018)

References	Ref (24)	Ref (25)	Ref (26)	Ref (27)	Ref (28)	Ref (29)	Ref (30)	Ref (31)	Ref (32)	Ref (33)	Ref (34)
Country	USA	USA	USA	Europe	Italy	China	China	China	USA	USA	China
Procedures	OPD *vs.* MIPD (LPD+RPD)	OPD *vs.* LPD	RAPD *vs.* OPD (other journals)	OPD *vs.* MIPD (LPD+RPD)	OPD *vs.* RPD	RPD	LPD	OPD *vs.* LPD	OPD *vs.* LPD	OPD *vs.* RPD	LPD
Publication date	2019	2018	2018	2018	2018	2018	2018	2018	2017	2017	2017
Inclusion period	2010–2015	2010–2013	2008–2014	OPD: 2014–2017; MIPD: 2012–2017	2007–2014	2011–2017	2013–2017	2014–2016	2010–2013	OPD: 2003–2015; RPD: 2011–2015	2012–2016
Single/multiple centers	Multiple, NCDB	Multiple, NCDB	Multiple	Multiple	Single	Single	Single	Single	multiple, NCDB	OPD: multiple, 16 centers; RPD: single	Single
Type of study	Retrospective, propensity weighting	Retrospective	Retrospective	Retrospective propensity score-matched cohort study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective propensity score-matched cohort study	Retrospective
Patient number	18,259 *vs.* 3,754	1,520 *vs.* 248	92 *vs.* 1,105	729 *vs.* 729	227 *vs.* 82	417	300	213 *vs.* 202	7,385 *vs.* 828	152 *vs.* 152	233
Female	48.22% *vs.* 48.32%	53.6% *vs.* 46.8%	53% *vs.* 41%–50%	49.8% *vs.* 49.0%	55.1% *vs.* 43.9%	52%	39%	40.8% *vs.* 42.6%	–	48.5%	38%
Age (year)	>60, 69.48% *vs.* 69.40%	>75, 100%, 79.6 *vs.* 79.5	65 *vs.* 66–69	64.6±11.7 *vs.* 64.5±11.6	67.4 (59.7–74.8) *vs.* 61.6 (51.9–70.7)*	53.99±14.04	59.5±9.6	55±11 *vs.* 54±12	65.7±10.4 *vs.* 65.9±10.7	64 (56–72)	60.3±13.0
BMI (kg/m^2)	–	–	25.8 *vs.* 21.5–23.7	24.8±4.0 *vs.* 24.9±4.2	24.8±0.2 *vs.* 23.5±0.4*	22.7±4.7	23.2±3.3	22±5 *vs.* 23±5	–	–	22.8±3.5
ASA classification	–	–	>III, 46% *vs.* 16%–20%	>3, 20.4% *vs.* 22.2%	>II, 65.6% *vs.* 41.5%*	–	–	>II, 18.8% *vs.* 21.8%	–	–	–
Tumor size (mm)	33.3±18.0 *vs.* 33.3±17.7	>4 cm, 21.6% *vs.* 19.8%	–	29.9±18.5 *vs.* 25.9±13.9	–	–	33	–	–	–	39±24
AJCC stage 1+2	92.98% *vs.* 93.16%	86.8% *vs.* 92.2%	–	T3–T4: 53% *vs.* 40%; N1–N2: 59.3% *vs.* 45.3%	–	–	–	–	89.9% *vs.* 100%	–	–
Operative time (min)	–	–	504 *vs.* (346–595)	324.2±93.9 *vs.* 415.8±110.9	450 (370–520) *vs.* 502 (450–566)*	300 (120–720)	402 (150–720)	320±91 *vs.* 301±175	–	–	368.0±57.4

Table 1 (*continued*)

Table 1 (*continued*)

References	Ref (24)	Ref (25)	Ref (26)	Ref (27)	Ref (28)	Ref (29)	Ref (30)	Ref (31)	Ref (32)	Ref (33)	Ref (34)
EBL (mL)	–	–	242 *vs.* (500–1,340)	–	782.4 (359.4–1,244.1) *vs.* 452.9 (183.6–713.9)*	100 (20–2,000)	500 (100–3,000)	390±301 *vs.* 194±107	–	–	203.8±138.6
Tumor type	Pancreatic cancer	Pancreatic cancer	Multiple	Pancreatic tumors, 62.1% *vs.* 62.8%	Multiple	Multiple	Multiple	Multiple	Pancreatic cancer	Multiple	Multiple
PDAC	100%	100%	26% *vs.* 43%–55%	47.3% *vs.* 42.1%	41.9% *vs.* 28.1%*	31.80%	23.00%	33.3% *vs.* 11.4%*	100%	Cancer + pancreatitis, 53.3% *vs.* 53.3%	36.00%
R0 rate	80.0% *vs.* 84.6%	73.0% *vs.* 77.4%	–	–	–	97%	99%	97.2% *vs.* 99.0%	76.8% *vs.* 79.1%	–	99%
Resected lymph nodes	>16, 45.2% *vs.* 48.1%	>10, 67.8% *vs.* 69.0%	–	–	–	14.9±6.7	13	10±5 *vs.* 10±5	17.1±9.6 *vs.* 18.1±9.5*	–	21.3±11.9
POPF (B/C)	–	–	9.8% *vs.* 9.6%–17.8 %	12.7% *vs.* 22.6%*	15.0% *vs.* 23.2%	9.35%	8.30%	3.8% *vs.* 4.5%	–	11.2% *vs.* 6.6%	6.90%
Major morbidity	–	–	–	30% *vs.* 28%	13.7% *vs.* 11.0%	13.20%	–	32.9% *vs.* 30.2%	–	23.7% *vs.* 23%	–
Mortality	90-day, 6.69% *vs.* 5.02%; 30-day, 3.69% *vs.* 3.29%	90-day, 12.2% *vs.* 7.2%*; 30-day, 5.9% *vs.* 4.9%	2.2% *vs.* 1.0%–3.5%	3.3% *vs.* 4.0%	6.2% *vs.* 3.7%	90-day, 1.61%; 30-day, 0.96%	4.30%	1.4% *vs.* 0.5%	90-day: 7.3% *vs.* 6.9%; 30-day: 3.8% *vs.* 4.1%	90-day: 1.3% *vs.* 3.3%	0.90%
Survival time (month)	–	15.6 *vs.* 19.8*	–	–	–	–	–	–	–	–	–
LOS (d)	>9, 43.8% *vs.* 35.1%*	10 *vs.* 10	10 *vs.* (7–22)	17.4±14.6 *vs.* 17.0±12.3	18 (14–28) *vs.* 18 (14–26)	–	17 (6–89)	19.2±7.1 *vs.* 13.0±7.2*	11.8±9.3 *vs.* 10.2±8.5*	11.8±10.6 *vs.* 10.5±6.9	18.1±11.2
Readmission	30-day: 8.04% *vs.* 8.2%	13.1% *vs.* 9.7%	–	12.6% *vs.* 9.8%	–	–	–	–	9.2% *vs.* 6.8%*	21.7% *vs.* 22.4%	–
Neoadjuvant chemotherapy	15.07% *vs.* 15.22%	9.7% *vs.* 6.6%	–	–	–	–	–	–	12.7% *vs.* 12.6%	–	–
Neoadjuvant radiation	7.43% *vs.* 7.61%	3.9% *vs.* 5.7%	–	–	–	–	–	–	7.2% *vs.* 6.7%	–	–
Adjuvant therapy	56.1% *vs.* 57.6%	36% *vs.* 35.9%	–	–	–	–	–	–	60.4% *vs.* 61.4%	–	–
Conversion rate	–	29.80%	–	15.80%	1.20%	4.56%	–	–	–	–	–
Annual case volume >10	61.4% *vs.* 64.4%	9.1% *vs.* 22.2%*	–	100%	Yes	Yes	Yes	Yes	LPD≥20, 25%	–	Yes

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on cancer; EBL, estimated blood loss; PDAC, pancreatic ductal adenocarcinoma; POPF (B/C), grade B and C postoperative pancreatic fistula; LOS, length of stay; LPD, laparoscopic pancreaticoduodenectomy; RPD, robotic pancreaticoduodenectomy; NCDB, American National Cancer Database. Outcomes are $\bar{x}\pm s$ or median (range); *, P<0.05.

Table 2 MIPD *vs.* OPD for pancreatic head cancer: safety, feasibility and outcomes (2012–2016)

Reference	Ref (23)	Ref (35)	Ref (36)	Ref (37)	Ref (38)	Ref (39)	Ref (40)	Ref (41)	Ref (42)	Ref (43)	Ref (44)	Ref (45)
Country	USA	USA	USA	USA	France	USA	USA	USA	China	USA	Germany	USA
Procedures	OPD *vs.* LAPD	OPD *vs.* MIPD (LPD+RPD)	OPD *vs.* LPD	OPD *vs.* RPD	OPD *vs.* LPD	OPD *vs.* MIPD (LPD+RPD)	OPD *vs.* LPD	OPD *vs.* RPD	OPD *vs.* RAPD	OPD *vs.* LPD	OPD *vs.* MIPD	OPD *vs.* LRPD
Published time	2014	2016	2016	2016	2015	2015	2015	2016	2015	2014	2014	2012
Inclusion period	2010–2013	2010–2012	1995–2014	2011–2015	2011–2014	2010–2011	2010–2011	2012–2013	2010–2013	2008–2013	1996–2013	2009–2010
Single/multiple lefts	Single	Multiple, NCDB	Single	Multiple: 8 high-volume lefts	Single	Multiple, NCDB	Multiple, NCDB	Single	Single	Single	Single	Single
Type of study	Retrospective case-matched study	Retrospective	Retrospective	Retrospective	Retrospective case-matched study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective case-matched study	Retrospective case-matched study
Patient number	25 *vs.* 28	6,776 *vs.* 1,191	193 *vs.* 58	817 *vs.* 211	46 *vs.* 46	6,078 *vs.* 983	4,037 *vs.* 387	49 *vs.* 22	120 *vs.* 60 cancer: 38 *vs.* 19	214 *vs.* 108	40 *vs.* 40	30 *vs.* 30
Female	68% *vs.* 61%	48.4% *vs.* 48.5%	50.3% *vs.* 44.8%	48% *vs.* 45%	39% *vs.* 43%	49% *vs.* 50%	–	62.9% *vs.* 59%	45.8% *vs.* 43.3%	39% *vs.* 53%*	63% *vs.* 63%	46% *vs.* 46%
Age (year)	65 (34–85) *vs.* 64 (45–84)	66.4 *vs.* 66.6	68.9 (33.3–86.9) *vs.* 69.9 (40.6–84.8)	65 (15–93) *vs.* 67 (15–86)	63 (47–81) *vs.* 60 (27–85)	65±11 *vs.* 66±12	66±10 *vs.* 66±11	63 (26–86) *vs.* 63 (38–82)	53.8±14.3 *vs.* 53.6±13.5	65±11 *vs.* 67±10	65 (31–82) *vs.* 63 (20–82)	61 *vs.* 62
BMI (kg/m^2)	23 *vs.* 28	–	25.6 (15.0–46.1) *vs.* 25.9 (17.7–49.6)	26.1 (14.7–85.5) *vs.* 27.5 (18.1–47.6)*	26 (19–42) *vs.* 23 (17–30)*	–	–	26.7 (16.2–38.2) *vs.* 25.5 (18.2–35.1)	22.6±3.4 *vs.* 23.2±2.7	27±5 *vs.* 27±5	25 (17–37) *vs.* 63 (20–83)	26 *vs.* 25
ASA classification	–	–	>3, 79.7% *vs.* 72.4%*	–	–	–	–	>2, 81.6% *vs.* 68.2%	>2, 1.6% *vs.* 1.7%	–	>2, 28% *vs.* 18%	>2, 76% *vs.* 53%
Tumor size (mm)	27 *vs.* 23	33.6 *vs.* 33.7	35 (3–140) *vs.* 25 (3–100)*	29 (0–50) *vs.* 25 (1–260)*	25 (15–40) *vs.* 28 (12–40)	34±28 *vs.* 34±37	33±24 *vs.* 32±13	31 (0–149) *vs.* 27 (15–60)	30±13 *vs.* 29±14	33±13 *vs.* 33±10	25 (6–35) *vs.* 25 (10–42)	29 *vs.* 30
AJCC stage 1+2	–	100% *vs.* 100%	96.8% *vs.* 98.3%	–	–	91% *vs.* 93%	94% *vs.* 97%	94.2% *vs.* 81.2%*	100% *vs.* 100%	–	–	–
Operation time (min)	347 *vs.* 355	–	375 (159–681) *vs.* 518 (313–761)*	300 (107–840) *vs.* 402 (257–685)*	264 (120–400) *vs.* 342 (240–540)*	–	–	364 (213–948) *vs.* 454 (294–529)*	2010–2012: 322±73 *vs.* 445±88* 2013: 324±92 *vs.* 340±98	388±92 *vs.* 379±94	410 (170–645) *vs.* 343 (212–510)	366 *vs.* 476*
EBL (mL)	454 (100–1,200) *vs.* 336 (100–1,400)	–	600 (50–7,800) *vs.* 250 (50–8,500)*	300 (20–7,350) *vs.* 200 (30–4,500)*	293 (50–12,00) *vs.* 368 (50–1,200)	–	–	650 (150–6,100) *vs.* 425 (50–2,200)*	2010–2012: 500 (400–800) *vs.* 500 (310–738); 2013: 500 (300–700) *vs.* 200 (100–450)*	867±734 *vs.* 492±519*	–	775 *vs.* 485

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Ref (23)	Ref (35)	Ref (36)	Ref (37)	Ref (38)	Ref (39)	Ref (40)	Ref (41)	Ref (42)	Ref (43)	Ref (44)	Ref (45)
Tumor type	Multiple	Pancreatic cancer	Pancreatic cancer	Multiple	Multiple	Pancreatic cancer	Pancreatic cancer	Multiple	Multiple	Pancreatic cancer	Multiple	Multiple
PDAC	64% *vs.* 57%	100%	100%	55% *vs.* 33%*	30% *vs.* 32%	86% *vs.* 85%	100%	61.2% *vs.* 68.2%	31.7% *vs.* 31.7%	100%	35% *vs.* 35%	46% *vs.* 46%
R0 rate	–	77.9% *vs.* 79.8%	79.8% *vs.* 84.5%	69% *vs.* 50%*	50% *vs.* 60%	No significant difference	74% *vs.* 80%	63.2% *vs.* 77.8%	92.1% *vs.* 94.7%	77% *vs.* 78%	86% *vs.* 86%	–
Resected lymph nodes	–	16.5±9.6 *vs.* 17.4±10.0*	17 (1–63) *vs.* 27 (9–70)*	19 (3–72) *vs.* 27 (7–65)*	25 (8–47) *vs.* 20 (8–59)	No significant difference	16±10 *vs.* 18±10*	–	17.8±7.1 *vs.* 18.1±6.6	20±8 *vs.* 21±8	19 (4–40) *vs.* 15 (7–33)	–
POPF (B/C)	28% *vs.* 18%	–	8.6% *vs.* 7.8%	9% *vs.* 14%*	Cancer: 29% *vs.* 20%	–	–	12.2% *vs.* 4.6%	15% *vs.* 8.3%	12% *vs.* 11%	28% *vs.* 18%	17% *vs.* 7%
Major morbidity	–	–	30.1% *vs.* 22.4%	24% *vs.* 24%	Cancer: 36% *vs.* 53%	–	–	20.4% *vs.* 13.6%	13.3% *vs.* 11.7%	13.6% *vs.* 5.6%	18% *vs.* 25%	43% *vs.* 30%
Mortality	–	90-day, 4.68% *vs.* 5.12%; 30-day, 2.42% *vs.* 2.69%	5.2% *vs.* 3.4%	90-day, 2.8% *vs.* 1.9%	Cancer: 0% *vs.* 0%	Cancer: 3.8% *vs.* 5.1%	4% *vs.* 5% LPD volume ≥ 10: 0.7% *vs.* 0%;LPD volume <10: 3.4% *vs.* 7.5%	4.1% *vs.* 0%	2.5% *vs.* 1.7%	30-day, 1% *vs.* 2%	0% *vs.* 5%	30-day, 0% *vs.* 4%
Survival time (month)	–	–	20.3 *vs.* 18.5	–	–	–	–	–	–	21.8 *vs.* 25.3	–	–
LOS (d)	9 *vs.* 7*	12.3±9.5 *vs.* 11.4±10.3*	9 (4–71) *vs.* 6 (4–68)*	8 (4–148) *vs.* 8 (4–58)	Cancer: 14 (7–32) *vs.* 15 (6–53)	No significant difference	12±9.7 *vs.* 10±8*	9 (5–48) *vs.* 7 (4–25)	25±11.2 *vs.* 20±7.4*	9 (5–73) *vs.* 6 (4–118)	16 (10–76) *vs.* 14 (6–59)	13 *vs.* 10*
Readmission	28% *vs.* 14%	9.5% *vs.* 8.7%	21.2% *vs.* 22.4%	23.5% *vs.* 30.8%*	9% *vs.* 9%	No significant difference	9% *vs.* 5%*	29.8% *vs.* 22.7%	–	–	–	–
Neoadjuvant chemotherapy	–	13.1% *vs.* 12.9%	–	–	–	–	12% *vs.* 11%	12.8% *vs.* 10%	–	14% *vs.* 11.1%	–	–
Neoadjuvant radiation	–	–	–	–	–	–	8% *vs.* 7%	–	–	–	–	–
Adjuvant therapy	–	52.7% *vs.* 55.3%	73.5% *vs.* 75.9%	–	–	–	–	–	–	76% *vs.* 76%	–	–
Conversion rate	Excluded	28%	–	Conversion to laparotomy: 4.7%	7.00%	30%	Excluded	13.60%	Conversion to LPD: 1.7%	6.50%	40%	10%
Annual case volume >10	No	–	Yes	Yes	Yes	73% *vs.* 47%	30%	Yes	Yes	Yes	Yes	Yes

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on cancer; EBL, estimated blood loss; PDAC, pancreatic ductal adenocarcinoma; POPF (B/C), grade B and C postoperative pancreatic fistula; LOS, length of stay; LPD, laparoscopic pancreaticoduodenectomy; RPD, robotic pancreaticoduodenectomy; NCDB, American National Cancer Database. Outcomes are $\bar{x}\pm s$ or median (range); *, P<0.05.

Overall, MIPD showed noninferiority in terms of EBL compared with OPD.

Postoperative morbidity and mortality are two crucial factors in evaluating the short-term outcomes of MIPD. Almost all the studies indicated that grade B and C postoperative pancreatic fistula (POPF) from MIPD and the major morbidity and mortality rates of MIPD were all similar to those of OPD. However, grade B and C POPF from MIPD were higher than those from OPD in only two multicenter studies — one from USA and the other from Europe (27,37). The other studies were all single-center studies or from the NCDB without POPF-related data. The American study enrolled 1,028 consecutive PDs (817 cases of OPD and 211 cases of MIPD) from 8 high-volume pancreatic centers. The MIPD group had a higher BMI, smaller tumor size, longer operative time and lower cancer patient ratios but less EBL and more harvested lymph nodes. The European case-matched cohort study enrolled 730 MIPD patients from 14 European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS) centers and 3,490 OPD patients from 53 high-volume centers. The baseline characteristics were well balanced, and the conclusions were convincing. Therefore, we believe that the major morbidity and mortality rates are comparable between MIPD and OPD; however, grade B and C POPF from MIPD are higher than those from OPD under the current conditions.

The length of hospital stay (LOS) and readmission of MIPD also showed noninferiority to OPD. Almost half of the studies focusing on the operation selection of pancreatic head cancer between OPD and MIPD indicated that MIPD showed a shorter LOS than OPD. In addition, the other studies showed no statistical significance between OPD and MIPD, which suggested that the LOS of MIPD was noninferior to OPD. Otherwise, MIPD did not increase the readmission rate compared with OPD in most studies. Therefore, patients undergoing MIPD for pancreatic head cancer could be benefited in terms of LOS and readmission, which might also decrease hospitalization expenses.

Long-term outcomes

Patients with pancreatic cancer usually have a poor long-term prognosis. The primary reason is that over 80% of patients have unresectable tumors. The 5-year overall survival rate of patients with resectable pancreatic cancer exceeds 20%, which is higher than that of patients with unresectable pancreatic cancer, which is less than 8%. Only a few studies have focused on the long-term outcomes between OPD and MIPD. Only 3 studies have reported the long-term prognosis of patients after undergoing MIPD (25,36,43) (*Table 3*). These studies are all retrospective and from the USA, one of which is a multicenter study that utilizes data from the NCDB. The baseline characteristics between patients undergoing OPD and those undergoing MIPD were well balanced. Chapman *et al*. (25) indicated that the overall survival time of MIPD was longer than that of OPD; however, the other two studies reached an alternative conclusion, namely, that the different survival time between OPD and MIPD was not significantly different. The probable reason for these conflicting conclusions was that all patients enrolled in the former study were elderly and over 75 years old. Elderly patients are often in poor physical condition, and therefore, they might benefit from MIPD over OPD. In addition, among the 3 studies, the R0 resection differences between OPD and MIPD were all unremarkable, which might be important for the long-term prognosis of patients with pancreatic head cancer. In summary, the current data on the differential long-term outcomes for pancreatic head cancer between OPD and MIPD are insufficient, and more multicenter, prospective studies focusing on long-term outcomes should be carried out in the near future.

Oncological outcomes

According to the TNM staging system, the tumor size and invasion of the regional lymph nodes are two crucial factors influencing the prognosis of pancreatic head cancer. The R0 resection rate and the number of resected lymph nodes will also affect the overall survival time of patients with pancreatic head cancer. Otherwise, neoadjuvant and adjuvant therapy have been reported to improve the prognosis of pancreatic head cancer; nevertheless, overall survival was not significantly prolonged. The tumor size in patients undergoing MIPD was similar to that in patients undergoing OPD in most studies, and the TNM staging distribution showed no statistical significance between the two procedures. Meanwhile, a similar proportion of patients undergoing MIPD and OPD received neoadjuvant and adjuvant therapy. Current studies indicated that MIPD showed noninferiority to OPD in terms of the R0 resection rate and the number of resected lymph nodes (*Table 4*). The superiority of MIPD in terms of resected lymph nodes was demonstrated in only 5 studies (32,35-37,40). The number of studies focusing on the survival time of patients with pancreatic head cancer after OPD or MIPD is

Table 3 MIPD *vs*. OPD for pancreatic head cancer: prognosis

References	Ref (25)	Ref (36)	Ref (43)
Country	USA	USA	USA
Procedures	OPD *vs*. LPD	OPD *vs*. LPD	OPD *vs*. LPD
Publication date	2018	2016	2014
Inclusion period	2010–2013	1995–2014	2008–2013
Single/multiple centers	Multiple, NCDB	Single	Single
Type of study	Retrospective	Retrospective	Retrospective
Patient number	1,520 *vs*. 248	193 *vs*. 58	214 *vs*. 108
Female	53.6% *vs*. 46.8%	50.3% *vs*. 44.8%	39% *vs*. 53%*
Age (year)	>75, 100%, 79.6 *vs*. 79.5	68.9 (33.3–86.9) *vs*. 69.9 (40.6–84.8)	65±11 *vs*. 67±10
BMI (kg/m^2)	–	25.6 (15.0–46.1) *vs*. 25.9 (17.7–49.6)	27±5 *vs*. 27±5
ASA classification	–	>3, 79.7% *vs*. 72.4%*	–
Tumor size (mm)	>4 cm, 21.6% *vs*. 19.8%	35 (3–140) *vs*. 25 (3–100)*	33±13 *vs*. 33±10
AJCC stage 1+2	86.8% *vs*. 92.2%	96.8% *vs*. 98.3%	–
R0 rate	73.0% *vs*. 77.4%	79.8% *vs*. 84.5%	77% *vs*. 78%
Resected lymph nodes	>10, 67.8% *vs*. 69.0%	17 (1–63) *vs*. 27 (9–70)*	20±8 *vs*. 21±8
Neoadjuvant chemotherapy	9.7% *vs*. 6.6%	–	14.0% *vs*. 11.1%
Neoadjuvant radiation	3.9% *vs*. 5.7%	–	–
Adjuvant therapy	36.0% *vs*. 35.9%	73.5% *vs*. 75.9%	76% *vs*. 76%
Survival time (month)	15.6 *vs*. 19.8*	20.3 *vs*. 18.5	21.8 *vs*. 25.3

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on cancer; LPD, laparoscopic pancreaticoduodenectomy; NCDB, American National Cancer Database. Outcomes are $\bar{x}\pm s$ or median (range); *, P<0.05.

insufficient, and the current conclusions are controversial and unconvincing. Therefore, a series of prospective multicenter studies should be performed to investigate whether patients with pancreatic head cancer could benefit from MIPD over OPD in terms of long-term oncological outcomes.

Differential outcomes in the USA, Europe and China

According to the above findings, MIPD is a safe and feasible new procedure for selecting patients with pancreatic head cancer, and it shows noninferiority to OPD in terms of short- and long-term outcomes as well as oncological outcomes. However, these conclusions might differ in different regions or countries. Herein, we analyze the differential outcomes reported in the USA, Europe and China (*Table 5*).

According to the data published on pancreatic head cancer, we found that MIPD was carried out in the USA earlier than in Europe and China and that the MIPD volume was higher, implying that surgeons in the USA are more proficient at MIPD than surgeons in Europe and China. The NCDB, which was founded in the USA in 2010, represents another advantage. This database is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society and contains approximately 34 million records from hospital cancer registries. The NCDB ensures the highest-quality, multidisciplinary and patient-centered cancer care. Based on this database, surgeons can obtain and analyze data on MIPD outcomes. Of note, this database does not have any surgical safety data, such as the operative time, EBL, prevalence of grade B and C POPF and major morbidity rates. Moreover, neoadjuvant therapy was discussed only in studies from the USA, when the NCDB was used, which may be due to the different MIPD indications between the USA and Europe and China. That is, patients with neoadjuvant therapy will be excluded from MIPD in Europe and China.

Unlike the USA, the volume of MIPD cases in Europe was relatively low. As shown above, the indications for MIPD in Europe were restricted to very specific, strict conditions only. In 2014, the Dutch Pancreatic Cancer Group (DPCG) launched the first multicenter LPD

Table 4 MIPD *vs*. OPD for pancreatic head cancer: oncological outcomes

Reference	Ref (24)	Ref (25)	Ref (32)	Ref (35)	Ref (36)	Ref (40)	Ref (43)
Country	USA	USA	USA	USA	USA	USA	USA
Procedures	OPD *vs*. MIPD (LPD+RPD)	OPD *vs*. LPD	OPD *vs*. LPD	OPD *vs*. MIPD (LPD+RPD)	OPD *vs*. LPD	OPD *vs*. LPD	OPD *vs*. LPD
Publication date	2018	2018	2017	2016	2017	2015	2014
Inclusion period	2010–2015	2010–2013	2010–2013	2010–2012	1995–2014	2010–2011	2008–2013
Single/multiple centers	multiple, NCDB	multiple, NCDB	multiple, NCDB	Multiple, NCDB	Single	Multiple, NCDB	Single
Type of study	Retrospective, propensity weighting	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Patient number	18,259 *vs*. 3,754	1,520 *vs*. 248	7,385 *vs*. 828	6,776 *vs*. 1,191	193 *vs*. 58	4,037 *vs*. 387	214 *vs*. 108
Annual case volume >10	61.4% *vs*. 64.4%	9.1% *vs*. 22.2%*	LPD ≥20, 25%	–	Yes	30%	Yes
Female	48.22% *vs*. 48.32%	53.6% *vs*. 46.8%	–	48.4% *vs*. 48.5%	50.3% *vs*. 44.8%	–	39% *vs*. 53%*
Age (year)	>60, 69.48% *vs*. 69.4%	>75, 100%, 79.6 *vs*. 79.5	65.7±10.4 *vs*. 65.9±10.7	66.4 *vs*. 66.6	68.9 (33.3–86.9) *vs*. 69.9 (40.6–84.8)	66±10 *vs*. 66±11	65±11 *vs*. 67±10
BMI (kg/m^2)	–	–	–	–	25.6 (15.0–46.1) *vs*. 25.9 (17.7–49.6)	–	27±5 *vs*. 27±5
ASA classification	–	–	–	–	≥3, 79.7% *vs*. 72.4%*	–	–
Tumor size (mm)	33.3±18 *vs*. 33.3±17.7	>4 cm, 21.6% *vs*. 19.8%	–	33.6 *vs*. 33.7	35 (3–140) *vs*. 25 (3–100)*	33±24 *vs*. 32±13	33±13 *vs*. 33±10
AJCC stage 1+2	92.98% *vs*. 93.16	86.8% *vs*. 92.2%	89.9% *vs*. 100%	100% *vs*. 100%	96.8% *vs*. 98.3%	94% *vs*. 97%	–
R0 rate	80% *vs*. 84.6%	73% *vs*. 77.4%	76.8% *vs*. 79.1%	77.9% *vs*. 79.8%	79.8% *vs*. 84.5%	74% *vs*. 80%	77% *vs*. 78%
Resected lymph nodes	>16, 45.2% *vs*. 48.1%	>10, 67.8% *vs*. 69%	17.1±9.6 *vs*. 18.1±9.5*	16.5±9.6 *vs*. 17.4±10.0*	17 (1–63) *vs*. 27 (9–70)*	16±10 *vs*. 18±10.0*	20±8 *vs*. 21±8
Neoadjuvant chemotherapy	15.07% *vs*. 15.22%	9.7% *vs*. 6.6%	12.7% *vs*. 12.6%	13.1% *vs*. 12.9%	–	12% *vs*. 11%	14.0% *vs*. 11.1%
Neoadjuvant radiation	7.43% *vs*. 7.61%	3.9% *vs*. 5.7%	7.2% *vs*. 6.7%	–	–	8% *vs*. 7%	–
Adjuvant therapy	56.1% *vs*. 57.6%	36.0% *vs*. 35.9%	60.4% *vs*. 61.4%	52.7% *vs*. 55.3%	73.5% *vs*. 75.9%	–	76% *vs*. 76%
Survival time (month)	–	15.6 *vs*. 19.8*	–	–	20.3 *vs*. 18.5	–	21.8 *vs*. 25.3

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on cancer; LPD, laparoscopic pancreaticoduodenectomy; RPD, robotic pancreaticoduodenectomy; NCDB, American National Cancer Database. Outcomes are $\bar{x}\pm s$ or median (range); *, $P<0.05$.

training program (Longitudinal Assessment and Realization of Laparoscopic Pancreatic Surgery 2, LAELAPS-2), which aimed to evaluate the safety, feasibility and outcomes of a multicenter training program for LPD. This program enrolled 114 patients undergoing LPD performed by 8 surgeons from 4 high-volume centers during 2014–2016. It was proven that the program was feasible and resulted in acceptable outcomes, with an 11% conversion rate, 43%

Table 5 Differential outcomes in USA, Europe and China

Country/ Region	Time MIPD initiated	MIPD volume for pancreatic head cancer	Number of studies	Advantages	Disadvantages
USA	20th century, the earliest	>3,700	14	1. Surgeons in USA are proficient at MIPD 2. NCDB, multicenter data on MIPD 3. Complete data on neoadjuvant therapy	Lack of surgical safety data
Europe	Later than USA	Approximately 1,000	4	1. Pan-European multicenter studies 2. The first report of a multicenter training program in LPD	1. Restrict indications for MIPD 2. The definition of high-volume center is unreasonable
China	2002	<1,000	5	1. The first expert consensus on LPD 2. R0 resection rate is higher than that of other countries	1. Lack of OPD control group 2. Lack of data on survival and neoadjuvant therapy 3. Lack of multicenter study

MIPD, minimally invasive pancreaticoduodenectomy; NCDB, American National Cancer Database; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

major morbidity rate, 15 median LOS, 4% 90-day mortality rate and 34% POPF rate (including grade A POPF) (46). As previously mentioned, a Pan-European multicenter propensity score-matched study was carried out to compare short-term outcomes between OPD and MIPD, and the results showed no differences between OPD and MIPD in terms of major morbidity and mortality rates and LOS. However, the grade B and C POPF rates from MIPD were higher than those from OPD (27). Therefore, the definition of a high-volume center might be unreasonable, and higher annual MIPD volumes are needed.

In China, an increasing number of surgeons are choosing MIPD as their first choice. Most studies are single-center retrospective studies that lack an OPD control group or survival and neoadjuvant therapy data (29,30,34). Expert consensus of LPD was issued by four pancreas surgery groups in China in 2017, which aimed to improve the safety and oncologic outcomes and promote the standardized development of LPD in China (47). This expert consensus highlighted the significance of a multidisciplinary team (MDT) and considered MDTs to be the basis of MIPD indications. In addition, studies from China showed a higher R0 rate than those from the USA and Europe, which was probably caused by differences in R0 resection standards and specimen collecting methods.

MIPD *vs.* OPD in enhanced recovery after surgery (ERAS)

The advantage of a minimally invasive procedure over an open procedure has been confirmed in terms of ERAS in many surgical fields, especially gastroenterology. However, whether MIPD is superior to OPD in terms of ERAS remains unknown. ERAS leads to less tissue damage, a shorter operative time, reductions in EBL, reductions in pain, a lower major morbidity rate, shorter LOS and lower costs. MIPD has been shown to be non-inferior to OPD in terms of EBL and major morbidities and superiority in terms of LOS and readmission rates (*Table 1*,*2*). In addition, a shorter LOS and lower readmission rate results in lower costs. Therefore, MIPD should show advantages over OPD in terms of ERAS. Recently, a study from Zureikat *et al*. (37) in the USA demonstrated that the implementation of ERAS was independently associated with cost savings for PD. ERAS and MIPD may synergistically optimize short-term outcomes, including the LOS and overall costs, compared with other combinations in the modern era (48).

Debate over MIPD

Although MIPD has shown noninferiority or superiority to OPD in terms of many short-term and long-term outcomes, there still remains some debate over comparisons of OPD with MIPD. First, selection bias can be found in most of the single-center studies, resulting in misleading conclusions. However, recent multicenter studies from the USA and Europe were case-matched studies whose baseline characteristics were well balanced. Therefore, the results from these studies are all relatively convincing. Second, there is a consensus that MIPD should be performed in high-volume centers. A large number of studies have demonstrated that the morbidity rate of MIPD is higher in low-volume centers than in high-volume centers. Notably, the definition of high-volume centers is

still controversial. Some surgeons believe that a high-volume center should perform more than 10 MIPDs annually, whereas others believe that 20 MIPDs should be the cut-off value. Other studies indicated that the learning curve of MIPD was longer than that of OPD and that a surgeon could be considered an expert after finishing a total of 40–60 MIPD procedures. The learning curve of OPD is also longer than that of other operations in general surgery (49,50). Therefore, the consensus of experts from China is that MIPD should be performed by experienced surgeons in high-volume centers with MDTs. The superior outcomes of high-volume centers cannot be achieved in low-volume centers. Hence, MIPD is still not recommended countrywide or worldwide. Further studies and guidelines should be issued by pancreatic surgeons across the world. Third, the conversion rate from MIPD to OPD is still high, which can be linked to the experience of surgeons and the slope of the MIPD learning curve. Stiles *et al*. indicated that the unplanned conversion from MIPD to OPD was associated with higher morbidity and 30-day mortality rates (51). Fourth, neoadjuvant therapy has been considered a complicating factor for surgeons performing MIPD. However, only studies from NCDB report data on neoadjuvant therapy. Therefore, further studies and clinical trials should be carried out to demonstrate the role of neoadjuvant therapy as a complicating factor in MIPD.

Conclusions

Pancreatic head cancer has a poor prognosis, and the standard operation, PD, is still the only potentially curative therapy for pancreatic head cancer. However, whether MIPD is superior to OPD for pancreatic head cancer in terms of safety, feasibility, short-term or long-term outcomes remains controversial. Based on the PD development history, staging and classification, as well as the European recommendations, we provided recommendations of indications for MIPD for pancreatic head cancer. By reviewing the MIPD-related literature *vs.* OPD-related literature, we concluded that MIPD showed noninferiority or superiority to OPD in terms of safety, feasibility, ERAS and several short-term and long-term outcomes. In addition, differential MIPD outcomes in the USA, Europe and China were analyzed by reclassifying the literature according to region or country. Among these three regions or countries, the USA performed MIPD the earliest and had the highest volume of MIPD cases. Another advantage of the USA is its possession of the NCDB, a powerful cancer database. The indications for MIPD in Europe were restricted to only very specific, strict conditions, and a series of multicenter MIPD training programs and case-matched studies were performed. Most of the studies conducted in China are single-center, retrospective studies that lack an OPD control group and survival and neoadjuvant therapy data. In addition, the R0 rate of MIPD in China is significantly higher than that in the USA and Europe, which was probably the result of different R0 resection standards and specimen collecting methods. Moreover, the selection bias, large number of low-volume centers, steep MIPD learning curve, high conversion rate and neoadjuvant therapy might limit the application of MIPD for pancreatic head cancer.

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Footnote

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