

REVIEW PAPER

The Miami International Evidence-Based Guidelines on Minimally Invasive Pancreas Resection

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Objective: The aim of this study was to develop and externally validate the first evidence-based guidelines on minimally invasive pancreas resection (MIPR) before and during the International Evidence-based Guidelines on Minimally Invasive Pancreas Resection (IG-MIPR) meeting in Miami (March 2019).

Summary Background Data: MIPR has seen rapid development in the past decade. Promising outcomes have been reported by early adopters from high-

volume centers. Subsequently, multicenter series as well as randomized controlled trials were reported; however, guidelines for clinical practice were lacking.

Methods: The Scottish Intercollegiate Guidelines Network (SIGN) methodology was used, incorporating these 4 items: systematic reviews using PubMed, Embase, and Cochrane databases to answer clinical questions, whenever possible in PICO style, the GRADE approach for assessment of the quality

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of evidence, the Delphi method for establishing consensus on the developed recommendations, and the AGREE-II instrument for the assessment of guideline quality and external validation. The current guidelines are cosponsored by the International Hepato-Pancreato-Biliary Association, the Americas Hepato-Pancreato-Biliary Association, the Asian-Pacific Hepato-Pancreato-Biliary Association, the European-African Hepato-Pancreato-Biliary Association, the European Association for Endoscopic Surgery, Pancreas Club, the Society of American Gastrointestinal and Endoscopic Surgery, the Society for Surgery of the Alimentary Tract, and the Society of Surgical Oncology.

Results: After screening 16,069 titles, 694 studies were reviewed, and 291 were included. The final 28 recommendations covered 6 topics; laparoscopic and robotic distal pancreatectomy, central pancreatectomy, pancreatoduodenectomy, as well as patient selection, training, learning curve, and minimal annual center volume required to obtain optimal outcomes and patient safety.

Conclusion: The IG-MIPR using SIGN methodology give guidance to surgeons, hospital administrators, patients, and medical societies on the use and outcome of MIPR as well as the approach to be taken regarding this challenging type of surgery.

Keywords: central pancreatectomy, distal pancreatectomy, guidelines, implementation, laparoscopic, left pancreatectomy, minimally invasive, pancreatoduodenectomy, robot, robot assisted, robotic, techniques, training, Whipple

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Minimally invasive pancreas resection (MIPR) comprises both laparoscopic and robotic pancreatic surgery. MIPR has seen rapid development in the last decade. Initially, early adopters from a few high-volume centers performed these procedures and reported promising outcomes.¹⁻⁸ Thereafter, multicenter series,⁹⁻¹³ and even

the first (monocenter and multicenter) randomized controlled trials¹⁴⁻¹⁷ were published and training programs were developed.¹⁸⁻²⁰ However, evidence-based guidelines for this field are still lacking. Evidence-based guidelines would not answer all relevant questions, but they should use a methodology to answer PICO-style questions and provide recommendations. The methodology used in this project employs the Scottish Intercollegiate Guidelines Network (SIGN), which incorporates the rigorous GRADE methodology on literature reviews and assign a score of the quality of evidence and strength of recommendations. SIGN is accredited by NICE (The National Institute for Health and Care Excellence).

The first International State-of-the-Art update meeting on MIPR was organized in São Paulo, during the IHPBA 2016 World Congress and was cosponsored with AHPBA. In the March 2017 issue of HPB, several articles reported the proceedings of this meeting.²¹⁻²⁹

The present evidence-based guidelines build on that experience. It does not try to repeat several of the topics already adequately addressed in São Paulo but delve into areas of controversy with additional evidence. The current guidelines are cosponsored by multiple international surgical societies and contains evidence on both laparoscopic (LDP) and robotic distal pancreatectomy (RDP), central pancreatectomy, pancreatoduodenectomy, as well as patient selection, training, learning curve, and minimal annual center volume to obtain optimal outcomes and patient safety.

METHODS

The present evidence-based guideline is a joint initiative of the International Hepato-Pancreato-Biliary Association (IHPBA), the Americas Hepato-Pancreato-Biliary Association (AHPBA), the

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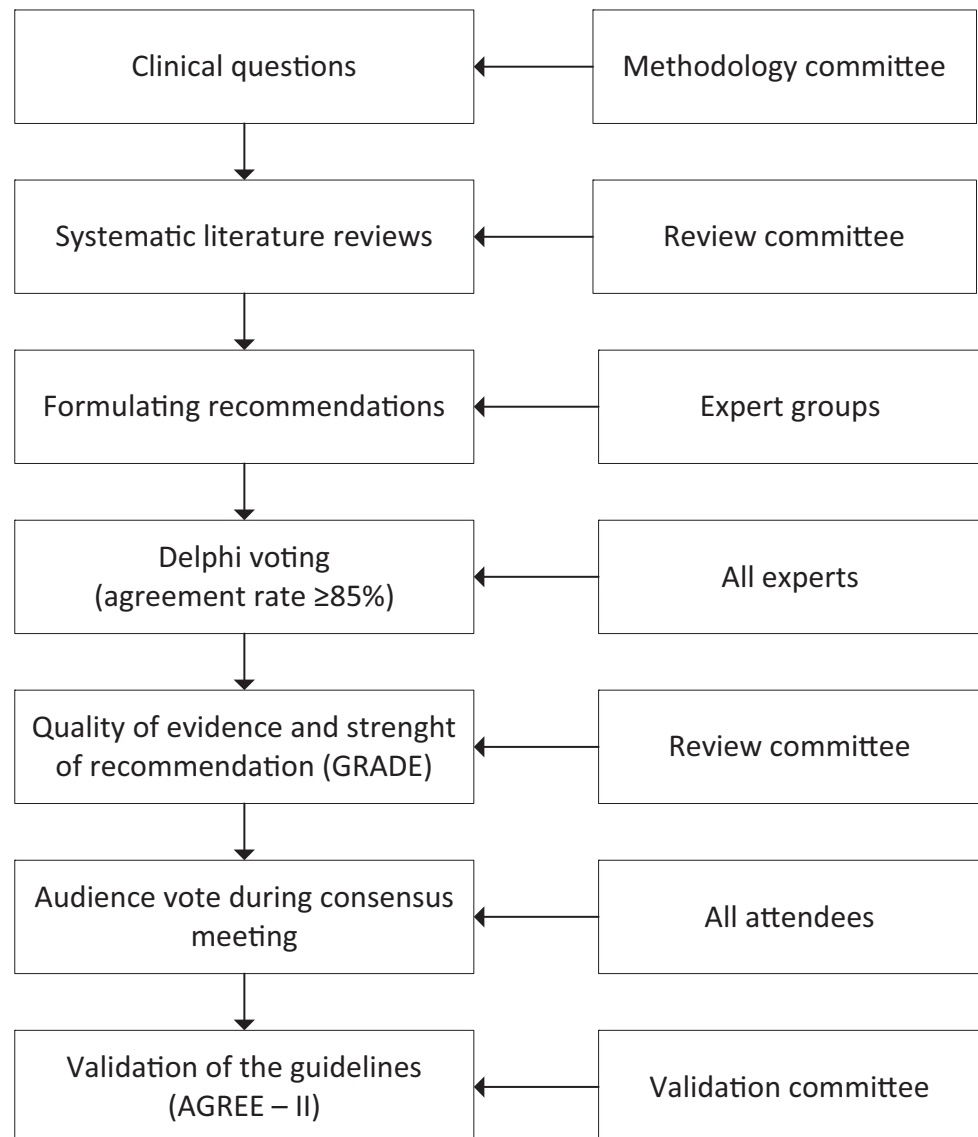


FIGURE 1. Flow chart of the guideline process.

Asian-Pacific Hepato-Pancreato-Biliary Association (A-HPBA), the European-African Hepato-Pancreato-Biliary Association (E-AHPBA), the Pancreas Club, the Society of American Gastrointestinal and Endoscopic Surgery (SAGES), the European Association for Endoscopic Surgery (EAES), the Society for Surgery of the Alimentary Tract, and the Society of Surgical Oncology and involves international experts (Supplementary Tables S1–S5, <http://links.lww.com/SLA/B781>).

The process and steps taken to reach the final recommendations are represented in Figure 1. A methodology committee identified the most important clinical questions, which were approved by the steering committee, and assigned expert review groups to evaluate each of these questions. Each group consisted of 2 to 5 MD/PhD students who performed systematic literature reviews and 5 to 8 experts in the field (Fig. 2). In October 2018, each group received a list of questions regarding their topic. The groups were encouraged to suggest changes and/or add relevant

questions based on their expertise and available literature. Furthermore, all members of the expert review groups were asked to take a tutorial on the SIGN method,³⁰ which incorporates the GRADE methodology.³¹

Once all questions were finalized by each group, the following steps were made to provide evidence-based recommendations and remarks:

- Literature review:** A systematic literature review was performed using PubMed, Embase, and Cochrane databases to include randomized trials, observational cohort studies, and systematic reviews with a minimum of 20 patients undergoing a MIPR published in English, and available in full text. SIGN methodology³⁰ was used to assess the quality of the evidence.
- Summary of studies:** A summary of each reviewed manuscript was completed, and a brief summary of the literature along with

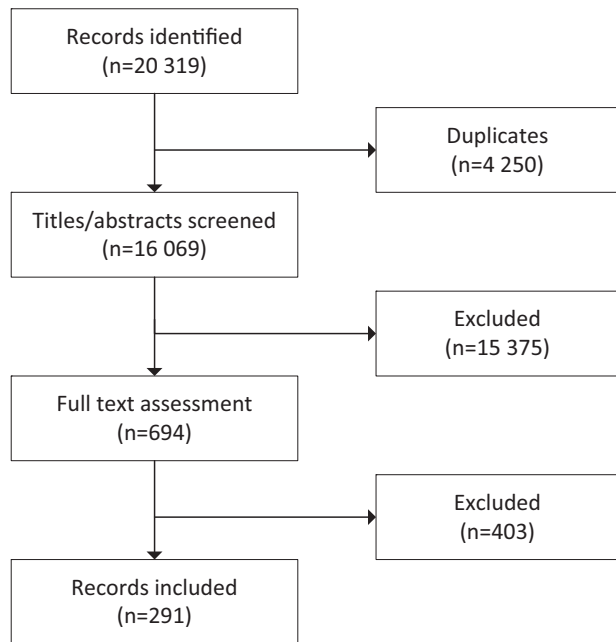


FIGURE 2. Flow chart of systematic literature review.

evidence tables were created for each question, aggregating the studies to facilitate answering the questions.

- (c) Recommendations: Recommendations were formulated based on the available evidence. All recommendations included a GRADE rating³¹ (see Tables 1 and 2) based on the quality of evidence and strength of recommendation.
- (d) Remarks: When deemed necessary, relevant remarks to enhance the recommendations were added.

- (e) Proposed actions: Given that there was insufficient literature for several of the recommendations, a proposed future action is formulated to emphasize research opportunities and improve the quality of evidence.

Each group submitted the above listed items (a–d) per question to the steering committee before December 31st, 2018. A synthesis of the work from different groups was completed in January 2019 by the chairs of the steering and methodology committee (H.A., M.G.B., and M.A.H.). The synthesis of the work was then distributed to all experts, for a first Delphi vote. The results of the Delphi vote were kept anonymous and reviewed by the chair (H.A.) who did not participate in the Delphi vote. Recommendations were approved if an agreement rate of $\geq 85\%$ was achieved. If the predefined rate of 85% was not reached, the recommendation, including feedback comments, was returned to the expert review group to amend accordingly. Subsequently, the amended recommendations that had not passed on the first Delphi round were sent to all experts for a second Delphi vote. The same approval process was followed. In the event that a recommendation would not pass the second Delphi round, plans were to go through a third Delphi on site at the International Evidence-based Guidelines on Minimally Invasive Pancreas Resection (IG-MIPR) meeting. On March 18 and 19, 2019, the evidence-based recommendations were presented and discussed during the IG-MIPR meeting in Miami Beach. Two additional processes took place during the meeting:

- (a) AGREE II: A validation committee used the AGREE II instrument³² to assess the quality of the guidelines. This committee consisted of 18 members that included open, laparoscopic, and robotic experts as well as administrators, a patient advocate representative, a methodologist, and a facilitator with prior experience on the process. To avoid bias, the committee members did not participate in the creation and had no prior knowledge of the guidelines. After attending each guideline presentation, they had private deliberations for a total of about

TABLE 1. GRADE Recommendations

Quality of evidence	1. Strong Recommendation	2. Weak Recommendation
A. High quality of evidence	1A. Benefits clearly outweigh risk and burdens, or vice versa	2A. Benefits closely balanced with risks and burdens
B. Moderate quality of evidence	1B. Benefits clearly outweigh risk and burdens, or vice versa	2B. Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks, and burdens
C. Low quality of evidence	1C. Benefits appear to outweigh risk and burdens, or vice versa	2C. Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens

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TABLE 2. Quality of Evidence in GRADE

A. High quality of evidence	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
B. Moderate quality of evidence	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
C. Low quality of evidence	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.

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6.5 hours throughout the meeting, using the AGREE methodology for each guideline statement.

- (b) All attendees were surveyed during the meeting about their agreement with the final recommendations via a web-based system. The results of this survey were added to the evidence-based recommendation to provide readers with insight into the level of support among attendees.

Thereafter, in April and May 2019, a combined document with all recommendations was created, which was circulated and approved by all the group leaders and finalized. In June 2019, the final draft of the manuscript containing the recommendations was reviewed and approved by all members of the steering expert, validation, and review committees before submitting the manuscript for publication.

RESULTS

The 6 main topics (A-F) are presented consecutively, incorporating 28 clinical questions (Q1–Q28) and their corresponding recommendations (Table 3). Each recommendation includes a GRADE (level of evidence and strength of recommendation), the expert agreement rate, the overall quality score of the validation committee according to AGREE-II, the IG-MIPR meeting audience agreement rate, and remarks, if appropriate. Agreement rates and quality scores given by the validation committee are expressed as medians with range in Supplementary Figure S1, <http://links.lww.com/SLA/B781>. The IG-MIPR meeting was attended by 117 surgeons from >20 countries.

Distal and Central Pancreatectomy

Q1. Should Minimally Invasive Distal Pancreatectomy Versus Open Distal Pancreatectomy Be Used Regardless of Indication, When Appropriate?

Recommendation. Q1a: Minimally invasive distal pancreatectomy (MIDP) for benign and low-grade malignant tumors is to be considered over open distal pancreatectomy (ODP), since it is associated with a shorter hospital stay, reduced blood loss, and equivalent complication rates (GRADE 1B, expert agreement 95.0%, quality score 85.0%, audience agreement 100.0%). Q1b: Prospective data about the cost effectiveness of MIDP compared to ODP are limited and require further studies (GRADE 2C, expert agreement 97.5%, quality score 85.0%, audience agreement 91.0%). Q1c: MIDP is associated with a better postoperative quality of life (QoL) than ODP (GRADE 2B, expert agreement 85.0%, quality score 85.0%, audience agreement 88.0%).

Comments. One multicenter randomized controlled trial (RCT) comparing MIDP with ODP reported a shorter hospital stay and reduced blood loss after MIDP, whereas the overall complication rate was similar,¹⁴ hereby confirming the findings of 10 systematic reviews and meta-analyses.^{33–42} Cost-effectiveness of LDP compared to ODP was reported in 2 studies and showed a similar or slightly decreased total hospital cost after LDP.^{43,44} The RCT and 1 case–control study showed a higher QoL during the first 30 days following MIDP.^{14,45} Results from three ongoing RCTs, the multicenter DIPLOMA trial (ISRCTN44897265), the monocenter LAPOP trial (ISRCTN26912858), and the multicenter “Study of Laparoscopic Versus Open Distal Pancreatectomy in Patients With Pancreatic Cancer at the Body and Tail” (NCT03792932), should increase the level of evidence available on this topic.

Proposed Action. Prospective trials and registries should be designed to evaluate cost and QOL outcomes. Participation in these trials is recommended.

Q2. Should MIDP Versus ODP Be Used for the Treatment of Pancreatic Ductal Adenocarcinoma?

Recommendation. MIDP for pancreatic ductal adenocarcinoma appears to be a feasible, safe, and oncologically equivalent technique in experienced hands, although prospective comparative studies are lacking (GRADE 2B, expert agreement 95.0%, quality score 87.0%, audience agreement 96.0%).

Comments. Three systematic reviews and meta-analyses suggested comparable oncological outcomes in terms of resection margin, 30-day mortality, disease-free survival, and overall survival between MIDP and ODP.^{37,46,47} One meta-analysis found a lower lymph node yield during MIDP,⁴⁷ whereas another meta-analysis found a similar lymph node yield in both approaches.³⁷ Results from the DIPLOMA trial and the “Study of Laparoscopic Versus Open Distal Pancreatectomy in Patients with Pancreatic Cancer at the Body and Tail” should increase the level of evidence available on this topic.

Proposed Action. Additional randomized trials, with special emphasis on oncological outcomes, should be designed and conducted to increase the level of evidence.

Q3. Should MIDP Versus ODP Be Used for the Treatment of Left-Sided Pancreatic Adenocarcinoma With Vascular Resection?

Recommendation. No evidence exists regarding the use of vascular resection in MIDP. To address this question, data on patient treatment and outcomes need to be entered in prospective registries and databases (EXPERT OPINION, expert agreement 97.5%, quality score 87.0%, audience agreement 98.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. Participation in retrospective and/or prospectively maintained database studies and registries is recommended.

Q4a. Should Staple Versus Another Type of Closure Be Used for Stump Closure in MIDP?

Recommendation. Both stapler and nonstapler closure can be used in MIDP, as outcomes are comparable (GRADE 1C, upgraded from 2C, expert agreement 100.0%, quality score 82.0%, audience agreement 86.0%).

Comments. Several studies reported the safety and feasibility of staple closure in single arm-series^{48,49} or noncomparative series between ODP and MIDP.^{50,51} Gradual compression stepwise closure should be encouraged.⁵²

Proposed Action. Additional randomized trials are to be considered to address the outcomes and cost of stump closure methods.

Q4b. Should Staple Line Reinforcement Versus no Reinforcement Be Used for Stump Closure in MIDP When a Stapler Is Used?

Recommendation. Evidence to support routine staple line reinforcement with any method or material is lacking (GRADE 2C, expert agreement 97.5%, quality score 82.0%, audience agreement 82.0%).

Comments. Data supporting the use of staple line reinforcement specific for MIDP are lacking. Two RCTs concerning the efficiency of Absorbable Fibrin Sealant Patch did not find a significant effect of the patch on the postoperative pancreatic fistula (POPF) rate, but MIDP and ODP were not separated.^{53,54} One retrospective study on MIDP found no differences in POPF rate between the group who received TachoSil and those who did not received the surgical patch.⁵⁵ Mesh reinforcement was suggested by 1 RCT to reduce the pancreatic fistula rate, but data on MIDP and ODP were not separated.⁵⁶

TABLE 3. Summary of Recommendations

		GRADE
Distal and Central Pancreatectomy		
1a	MIDP for benign and low-grade malignant tumors is to be considered over ODP since it is associated with a shorter hospital stay, reduced blood loss, and equivalent complication rates.	1B
1b	Prospective data about the cost effectiveness of MIDP compared to ODP is limited and requires further studies.	2C
1c	MIDP is associated with a better postoperative quality of life than ODP.	2B
2	MIDP for pancreatic ductal adenocarcinoma appears to be a feasible, safe, and oncologically efficient technique in experienced hands, although prospective comparative studies are lacking.	2B
3	There is no evidence regarding the use of vascular resection in MIDP. To address this question data on patients' treatment and outcomes need to be entered in prospective registries and databases.	Expert opinion
4a	Both stapler and nonstapler closure can be used in MIDP as outcomes are comparable.	2C
4b	Evidence to support routine staple line reinforcement with any method or material is lacking.	2C
5	No studies exist specifically comparing minimally invasive spleen-preserving distal pancreatectomy with open spleen-preserving distal pancreatectomy.	2C
6	Both laparoscopic and robotic distal pancreatectomy are safe and feasible options. The use of either technique should be based on surgeons' experience and local resources.	2B
7a	The feasibility of minimally invasive central pancreatectomy has been reported, but the safety needs to be confirmed before promoting its wide adoption. Studies comparing minimally invasive versus open central pancreatectomy are inadequate in quality and quantity.	1C
7b	Minimally invasive enucleation of pancreatic lesions in selected patients is an appropriate alternative to open enucleation.	2B
Pancreatoduodenectomy		
8	There is insufficient data to recommend MIPD over OPD. Centers performing MIPD should be including all their MIPD outcomes data into national and international registries, and prospectively maintained pancreas databases.	2A
9	Both MIPD and OPD are valid approaches for selected patients with adenocarcinoma.	2B
10	No comparative data regarding MIPD vs OPD after neoadjuvant therapy exists and further investigation is warranted.	Expert opinion
11	Limited comparative data regarding vascular resection in MIPD vs OPD exist and further investigation is warranted. MIPD with vascular resection should only be performed by highly experienced surgeons and in high-volume centers.	1C
12	No evidence of superiority between LPD and RPD exists. Surgeon training, experience, and available resources currently guide which approach is utilized.	2C
Patients and technique		
13	There are no contraindications for MIPR based on patient age, obesity or previous abdominal surgery.	1C
14	The evidence to suggest a relationship between comorbidity and the outcome of MIPR is limited in quality and quantity.	2C
15	No evidence exists which specifically addresses the relative benefits of any particular hemostatic technique in MIPR	1C
16	No evidence exists to clearly determine the appropriate timing or indication for conversion in MIPR. Elective conversion should be considered based on surgeon experience, concern for patient safety or failure to progress. The surgeon is expected to have expertise in various methods to control bleeding in the event of hemorrhage that may require urgent conversion	1C
Implementation and training		
17	The value of formal MIPR training is the safe introduction and expansion of MIPR. Participation in a structured training program is strongly recommended for all surgeons undertaking MIPR. A structured MIPR training program may include virtual reality simulation, inanimate biotissue models to practice dissection and anastomotic techniques, surgical video review, on-site proctoring, and remote tele-mentorship.	1C
18	The annual individual surgeon's volume affects individual surgeon's outcomes. Single surgeon learning curves for MIPR show improvements in operative time, blood loss, lymph node harvest and complications with increased total volume/experience; however, the exact number remains to be defined.	2C
19	No specific studies assess prerequisites for MIPR. Experience in pancreatic surgery, including a formal fellowship training or an established practice as a pancreatic surgeon, is advised. A two-surgeon approach can be beneficial in the learning curve, although comparative evidence is lacking	1C
20	Center volume strongly affects outcomes after MIPR and consideration of total pancreas resection volume along with MIPR-specific volume is critical. MIPD should be performed in high-volume centers since mortality (centers <10 MIPD/year) and morbidity (centers <20 MIPD/year) are worse when performed in a low-volume setting.	1B
21	No specific evidence exists on requirements for an MIPR program. However, centers undertaking MIPR should consider including the following components: implementation of dedicated individual and team training, having >1 surgeon performing MIPR at the Institution, monitoring outcomes of MIPR for quality assurance, consideration of surgeon/institution volume of pancreas resections including MIPR	2C

TABLE 3. (Continued)

		GRADE
Instrumentation		
22	No documented advantages for any specific energy device have been reported.	Expert opinion
23	The development of instruments and enhanced visualization systems for MIPR should be encouraged.	Expert opinion
Accountability		
24	There are currently several registries for MIPR in development. The inclusion of patient data into thoughtfully organized and maintained regional, national and international registries supported by Hepato-Pancreato-Biliary organizations is strongly encouraged to follow trends and outcomes, and to assess quality.	Expert opinion
25	Outcome monitoring of MIPD is essential for its safe and wide expansion. Inclusion into validated regional, national and international registries is highly recommended.	Expert opinion
26	The development and the expansion of MIPR should be encouraged and monitored by national and international societies through the promotion of specific working groups who will drive training and registries to ensure patient safety and quality improvement.	Expert opinion

Proposed Action. In addition to the action plan for question Q4a, future randomized trials should assess staple line reinforcement and type of stapler.

Q5. Should Minimally Invasive Spleen-Preserving Distal Pancreatectomy Versus Open Spleen-Preserving Distal Pancreatectomy Be Used?

Recommendation. No studies exist specifically comparing minimally invasive spleen-preserving distal pancreatectomy with open spleen-preserving distal pancreatectomy (GRADE 2C, expert agreement 100.0%, quality score 90.0%, audience agreement 98.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. Prospective database studies and registries should compare minimally invasive and open spleen-preserving distal pancreatectomy.

Q6. Should LDP Versus RDP Be Used for the Treatment of Left-Sided Pancreatic Lesions?

Recommendation. Both laparoscopic and robotic distal pancreatectomy are safe and feasible options. The use of either technique should be based on surgeons' experience and local resources (GRADE 1B, upgraded from 2B, expert agreement 100.0%, quality score 83.0%, audience agreement 96.0%).

Comments. Four meta-analyses and 1 propensity score-matched study suggested comparable surgical outcomes between laparoscopic and robotic distal pancreatectomy in terms of POPF rate^{57–61} and overall morbidity.^{57–59,62} Spleen-preservation rates might be higher during robotic pancreatectomy^{57,58,60} or at least similar.^{59,61} The oncological outcomes are not different between these modalities.^{58,63,64}

Proposed Action. A randomized trial comparing LDP with RDP should be initiated, with special consideration to intraoperative complications, spleen preservation, and cost analysis.

Q7a. Should Minimally Invasive Central Pancreatectomy Versus Open Central Pancreatectomy Be Used?

Recommendation. The feasibility of minimally invasive central pancreatectomy has been reported, but the safety needs to be confirmed before promoting its wide adoption. Studies comparing minimally invasive versus open central pancreatectomy are inadequate in quality and quantity (GRADE 1C upgraded from 2C, expert agreement 97.5%, quality score 84.0%, audience agreement 85.0%).

Comments. One cohort study compared minimally invasive to open central pancreatectomy and found a comparable complication

rate with a shorter hospital stay in the minimally invasive group.⁶⁵ When comparing minimally invasive central pancreatectomy with laparoscopic extended distal pancreatectomy, the complication rate was higher, but the rate of new-onset diabetes mellitus was lower. A single-arm study reported an overall POPF rate of 51.0% after laparoscopic central pancreatectomy.⁶⁶

Proposed Action. Prospective database studies and registries should be employed to improve the quality of evidence on this topic.

Q7b. Should Minimally Invasive Enucleation Versus Open Enucleation of Pancreatic Lesions Be Used?

Recommendation. Minimally invasive enucleation of pancreatic lesions in selected patients is an appropriate alternative to open enucleation (GRADE 2B, expert agreement 97.5%, quality score 84.0%, audience agreement 92.0%).

Comments. Two meta-analyses compared minimally invasive with open enucleation and reported a shorter operative time, a shorter hospital stay, and comparable morbidity for the minimally invasive approach.^{67,68} Open enucleation was mainly chosen for deep or posterior lesions,⁶⁹ larger or multiple tumors,⁷⁰ or expected malignancy.^{70,71}

Proposed Action. Prospective database studies and registries are encouraged to improve the level of evidence on this topic.

Pancreatoduodenectomy

Q8. Should Minimally Invasive Pancreatoduodenectomy Versus Open Pancreatoduodenectomy Be Used Regardless of Indication, When Appropriate?

Recommendation. Insufficient data exist to recommend minimally invasive pancreatoduodenectomy (MIPD) over open pancreatoduodenectomy (OPD). Centers performing MIPD should be including all of their MIPD outcomes data into national and international registries, and prospectively maintained databases (GRADE 2A, expert agreement 90.0%, quality score 39.0%, audience agreement 92.0%).

Comments. Three RCTs comparing LPD to OPD have been published.^{15–17} Two single-center RCTs reported a shorter hospital stay in LPD.^{16,17} The 1 multicenter RCT showed no difference in outcomes but was prematurely stopped because of safety concerns as a result of higher 90-day mortality in the LPD group ($P = 0.2$).¹⁵ In this trial, the major complication (Clavien-Dindo ≥ 3) rate was comparable between the 2 approaches.¹⁵ LPD was found to have a longer operative time. Short-term outcomes, mortality rates, overall costs, 30-day, and 90-day morbidity seem similar between MIPD and

OPD.^{5,6,12,13,15–17,72–111} Literature suggests MIPD should be limited to experienced surgeons in high-volume centers because of the long learning curve and the difficulty of the procedure.^{5,13,72,90,104,105}

Proposed Action. Surgical societies should mandate centers performing MIPD and/or OPD to maintain a prospective database. To facilitate comparative analysis, additional randomized trials comparing MIPD and RPD, to OPD are encouraged. Trials should be performed only in centers where the MIPD learning curve has been completed.

Q9. Should MIPD Versus OPD Be Used for the Treatment of Periapillary Adenocarcinoma and Pancreatic Ductal Adenocarcinoma?

Recommendation. Both MIPD and OPD are valid approaches for selected patients with adenocarcinoma (GRADE 2B, expert agreement 92.5%, quality score 59.0%, audience agreement 91.0%).

Comments. Oncological outcomes are similar for the 2 approaches.^{78,80,89,98,99,104} No difference has been observed in overall survival, 30- and 90-day mortality.^{78,84,95} In 1 series, the progression-free survival was reported to be longer in MIPD.⁷⁸

Proposed Action. As per Q8.

Q10. Should MIPD Versus OPD Be Used for the Treatment of Pancreatic Head Adenocarcinoma After Neoadjuvant Therapy?

Recommendation. No comparative data exist, and further investigation is warranted (Expert Opinion, downgraded from 2C, expert agreement 100.0%, quality score 30.0%, audience agreement 87.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. Centers with prospectively maintained databases that have experience with post-neoadjuvant MIPD are encouraged to address this question.

Q11. Should MIPD Versus OPD Be Used for the Treatment of Pancreatic Head Ductal Adenocarcinoma Requiring Vascular Resection?

Recommendation. Limited comparative data exist, and further investigation is warranted. MIPD with vascular resection should only be performed by highly experienced surgeons and in high volume centers (GRADE 1C, upgraded from 2C, expert agreement 95.0%, quality score 41.0%, audience agreement 93.0%).

Comments. A retrospective cohort study reported comparable major complication rates after LPD and OPD with major vascular resection. However, in the OPD group, a higher proportion of complex segmental resections and repairs was performed compared with LPD.⁷⁹

Proposed Action. Centers with prospectively maintained databases that have experience with MIPD vascular resections are encouraged to address this question. Special attention should be given to late complications related to anastomosis quality, such as thrombosis and need for reintervention.

Q12. Should LPD Versus RPD Be Used for the Treatment of Pancreatic Head Lesions?

Recommendation. No evidence of superiority between LPD and RPD exists. Surgeon training, experience, and available resources currently guide which approach is utilized (GRADE 2C, expert agreement 95.0%, quality score 70.0%, audience agreement 98.0%).

Comments. Adequate comparisons of outcomes for LPD and RPD are limited in quantity and quality. Overall perioperative and short-term oncological outcomes are comparable with small, inconsistent differences reported between studies.^{91,112–115}

Proposed Action. Randomized controlled trials comparing LPD with RPD are to be considered in high-volume centers by surgeons beyond the learning curve for each approach.

Patients and Technique

Q13. Are There Contraindications for MIPR, Related to Patient Age, obesity, or Complex Previous Abdominal Operations?

Recommendation. There are no contraindications for MIPR based on patient age, obesity, or previous abdominal surgery (GRADE 1C, upgraded from 2C, expert agreement 97.5%, quality score 70.0%, audience agreement 98.0%).

Remark. Visceral obesity and major abdominal surgery may increase operative time, surgical difficulty, and conversion rate. Relative contraindications do exist based on surgeon experience, comfort, center volume, and experience as well as intraoperative findings (eg, pancreatitis, high-risk pancreas) and events. These relative contraindications are especially relevant in the early experience of MIPR and in low-volume centers with less experience in pancreatic surgery.

Comments. In elderly patients, outcomes between MIPR and the open approaches are comparable.^{103,110,116–118} When comparing obese patients with normal weight patients undergoing LDP, obese patients had an increased operative time and blood loss, whereas POPF and major complication rates were comparable.¹¹⁹ When comparing RPD versus OPD in obese patients, those undergoing RPD had a shorter operative time, less estimated blood loss, and a lower POPF rate.⁸³ In a case-matched study comparing patients with previous upper abdominal surgery to patients without such previous surgery, no differences were found.¹²⁰

Proposed Action. Prospective database studies and registries should improve the quality of evidence on this recommendation.

Q14. Does MIPR Offer Advantages Over the Open Approach for Patients With Elevated Comorbidity?

Recommendation. The evidence to suggest a relationship between comorbidity and the outcome of MIPR is limited in quality and quantity (GRADE 2C, expert agreement 97.5%, quality score 55.0%, audience agreement 75.0%).

Comments. One study compared LDP with ODP and performed subgroup analyses in high-risk patients (ASA III–IV). The high-risk LDP group (n = 15) showed a shorter operative time, less blood loss, a higher rate of spleen preservation, fewer complications, and a shorter hospital stay compared with high-risk ODP (n = 32).¹²⁰

Proposed Action. Centers with prospectively maintained databases should compare both approaches, stratify, and do subgroup analysis according to patient comorbidity. A comorbidity index specific for pancreatic surgery should be developed and validated.

Q15. What Are the Optimal Techniques for Control of Hemorrhage During MIPR?

Recommendation. No evidence exists which specifically addresses the relative benefits of any particular hemostatic technique in MIPR (GRADE 1C, upgraded from 2C, quality score 50.0%, audience agreement 89.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. Experienced surgeons with low intraoperative bleeding rates should publish their techniques of prevention and control of bleeding. A collaborative expert opinion manuscript is encouraged.

Q16. When Should a Surgeon Consider Conversion to an Open Approach (Contributing Factors and Timing of Conversion)?

Recommendation. No evidence exists to clearly determine the appropriate timing or indication for conversion in MIPR. Elective conversion should be considered based on surgeon experience, concern for patient safety, or failure to progress. The surgeon is expected to have expertise in various methods to control bleeding in the event of hemorrhage that may require urgent conversion (GRADE 1C, upgraded from 2C, expert agreement 97.5%, quality score 38.0%, audience agreement 100.0%).

Comments. Risk factors associated with an increased conversion rate are smoking, elevated BMI, surgeon case experience, and malignancy.^{121–126} No studies specifically assessed the timing of conversion.

Proposed Action. Authors are encouraged to record reasons for conversion, elective/preemptive versus urgent, and timing of conversion.

Training and Implementation

Q17. What Is the Value of Formal MIPR Training?

Recommendation. The value of formal MIPR training is the safe introduction and expansion of MIPR. Participation in a structured training program is strongly recommended for all surgeons undertaking MIPR. A structured MIPR training program may include virtual reality simulation, inanimate biotissue models to practice dissection and anastomotic techniques, surgical video review, on-site proctoring, and remote tele-mentorship (GRADE 1C, upgraded from 2C, expert agreement 97.5%, quality score 79.0%, audience agreement 95.0%).

Comments. Training programs for MIDP,¹⁸ LPD,¹⁹ and RPD²⁰ have been described. A steep increase in the use of MIDP was seen after training, and blood loss and conversion rate decreased.¹⁸ Surgical outcomes of LPD during and after training were in line with those of OPD.¹⁹ The training program for RPD describes a structured training that consists of the following steps: virtual reality simulation, biotissue curriculum, video library training, intraoperative evaluation, and skill maintenance with ongoing assessment.²⁰ The evaluation of the RPD training program showed that fellows increasingly performed a complete procedure.¹²⁷ The first 2 steps of the RPD training program are reported separately; step 1 is a virtual reality robotic simulation curriculum¹²⁸ and step 2 a biotissue drill on the robot simulating the steps of PD.¹²⁹ Both show improvement of outcomes after completing these steps.

Proposed Action. HPB training programs should specify whether MIS is part of their curriculum and if so, formalize its structure.

Q18. Does Surgeon Volume Affect Outcomes After MIPR?

Recommendation. The annual individual surgeon's volume affects individual surgeon's outcomes. Single surgeon learning curves for MIPR show improvements in operative time, blood loss, lymph node harvest, and complications with increased total volume/experience; however, the exact number remains to be defined (Grade 2C, expert agreement 95.0%, quality score 77.0%, audience agreement 96.0%).

Comments. Depending on the outcome that was used to assess the learning curve, 10 to 40 cases have been described to be required to reach proficiency in LDP.^{66,130–136} For RDP, the number of cases described is 7 to 37.^{131,137,138} In LPD learning curve, related

improvements in outcome were seen after 10–50 cases.^{66,139–142} For RPD, 20 to 40 cases have been described as needed to overcome the learning curve.^{74,138,143,144} Data on annual surgeon volume are not available.

Proposed Action. More studies are needed to address the optimal metric to assess the minimum number of cases needed to accomplish competency and good outcomes. Multi-institutional studies and registries are likely the best sources of data. Outcomes and video assessment studies are encouraged.

Q19. Are There Recommended Prerequisites for Surgeons Embarking on MIPR? Should the Presence of a Second Surgeon Be Required During Early Learning Curve?

Recommendation. No specific studies assess prerequisites for MIPR. Experience in pancreatic surgery, including a formal fellowship training or an established practice as a pancreatic surgeon, is advised. A 2-surgeon approach can be beneficial in the learning curve, although comparative evidence is lacking (GRADE 1C, upgraded from 2C, expert agreement 97.5%, quality score 77.0%, audience agreement 98.0%).

Comments. No evidence exists on a 2-surgeon approach in MIPR. A study comparing outcomes of LDP performed by expert surgeons and surgeons in training reports comparable outcomes.¹⁴⁵

Proposed Action: Centers performing MIPR are recommended to participate in prospective registries and include these data points.

Q20. Does Center Volume Affect Outcomes of MIPR?

Recommendation. Center volume strongly affects outcomes after MIPR and consideration of total pancreas resection volume along with MIPR specific volume is critical. MIPD should be performed in high volume centers since mortality (for centers performing <10 MIPD/year) and morbidity (for centers performing <20 MIPD/year) are worse when performed in a low volume setting (GRADE 1B, expert agreement 97.5%, quality score 82.0%, audience agreement 85.0%).

Comments. Center volume is associated with morbidity^{105,146} and mortality^{72,104,147} when PD^{104,105,147} and MIPD volume are analyzed.^{72,146} A decreased complication rate was seen in centers performing >20 MIPD/year¹⁴⁶ or >20 total PD/year.¹⁰⁵ Mortality rates decreased from an annual volume of >10 total PD or MIPD.^{72,104,147}

Proposed Action. Centers performing MIPR are recommended to participate in prospective registries. As a result, more data regarding center volume and outcomes will become accessible.

Q21. What Are Essential Requirements for a MIPR Program?

Recommendation. No specific evidence exists on requirements for a MIPR program. However, centers undertaking MIPR should consider including the following components: implementation of dedicated individual and team training, having >1 surgeon performing MIPR at the institution, monitoring outcomes of MIPR for quality assurance, consideration of surgeon/institution volume of pancreas resections including MIPR (GRADE 2C, upgraded from EXPERT OPINION, expert agreement 97.5%, quality score 75.0%, audience agreement 93.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. Centers and surgeons embarking in MIPR should use these guidelines as they develop a new MIPR program.

Instrumentation

Q22. Do Safety Advantages Exist for Specific Energy Devices?

Recommendation. No documented advantages for any specific energy device have been reported (GRADE expert opinion, downgraded from 2C, expert agreement 100.0%, quality score 51.0%, audience agreement 96.0%).

Comments. No literature addressing this topic was identified.

Proposed actions: Each surgeon should use the energy device they favor and are most familiarized with.

Q23. Does a Need Exist to Develop New Instrumentation for MIPR?

Recommendation. The development of instruments and enhanced visualization systems for MIPR should be encouraged (EXPERT OPINION, downgraded from 2C, expert agreement 97.5%, quality score 63.0%, audience agreement 89.0%).

Comments. Two studies regarding the use of augmented reality in pancreatic surgery concluded that this approach might increase surgical efficacy.^{148,149}

Proposed Action. Cooperation between surgeons and industry should be encouraged for the production of specific instrumentation for MIPR.

Accountability

All recommendations regarding accountability are based on expert opinion, as a result of lacking evidence.

Q24. What is the Current Status and Value of Registries for MIPR?

Recommendation. There are currently several registries for MIPR in development. The inclusion of patient data into thoughtfully organized and maintained regional, national, and international registries supported by HPB organizations is strongly encouraged to follow trends and outcomes, and to assess quality (EXPERT OPINION, expert agreement 100.0%, quality score 82.0%, audience agreement 100.0%).

Comments. No literature addressing this topic was identified. Several registries have been established on the last 5 years and served as the source for multiple MIPR-related reports.

Proposed actions: Surgical societies and pancreatic surgery consortiums should consider raising awareness on the benefits of participating in a registry and award some type of recognition to the participant institutions.

Q25. For MIPD, Should It Be Mandatory to Follow Outcomes and Belong to a Registry?

Recommendation. Outcome monitoring of MIPD is essential for its safe and wide expansion. Inclusion into validated regional, national, and international registries is highly recommended (Expert Opinion, expert agreement 100.0%, quality score 82.0%, audience agreement 98.0%).

Comments. No literature addressing this topic was identified.

Proposed Action. It should be mandatory and considered standard of care to follow outcomes in a prospectively-maintained database for centers performing MIPD. This recommendation should also be applied to OPD.

Q26. What Should Be the Role of Surgical Societies in the Development and Implementation of MIPR?

Recommendation. The development and the expansion of MIPR should be encouraged and monitored by national and

international societies through the promotion of specific working groups who will drive training and registries to ensure patient safety and quality improvement (Expert Opinion, expert agreement 97.5%, quality score 82.0%, audience agreement 100.0%).

Comments. No literature addressing this topic was identified.

Proposed Action: Creation and implementation of international and national MIPR working groups should occur within existing HPB societies and chapters.

DISCUSSION

MIPR has seen rapid development over the past decade and outcomes, particularly for MIPD, have varied significantly. Although experienced centers have reported excellent outcomes, suboptimal results have also been reported, and there are multiple anecdotal accounts of poor outcomes that are not recorded in the literature. This variance calls for attention to the lack of directives on how to appropriately train, safely implement, and expand MIPR.

One should not expect the current evidence-based guidelines would address and solve all issues related to MIPR. They should rather be seen as a progressive step in what hopefully would be a continuous international collaborative effort for the unbiased assessment and appropriate dissemination of MIPR. These guidelines also underline areas in which further research and development are needed.

It appears that open, laparoscopic, and robotic pancreas resections are all here to stay. The first randomized trials are now available, which compare outcomes between these approaches. Apart from designing new randomized trials, future studies should also help us better understand the role that each approach plays.

More importantly, future studies should focus on how these technical advances can make the operation better and reduce known complications such as pancreatic fistula, delayed gastric emptying, and infections.

The IG-MIPR meeting was organized to review the available evidence, design evidence-based recommendations among a wide range of open, laparoscopic, and robotic international pancreas experts, and develop specific guideline statements through a rigorous methodology. The guidelines have been endorsed by nine major surgical societies who participated in the planning and execution of the meeting. This process illustrates a true international collaborative effort with a group of experts from >20 countries.

During the first Delphi, only 3 recommendations did not reach 85% consensus among the 40 voting experts (4b, 14b, and 18). Per the established methodology, validation committee members, reviewers, and the chair of IG-MIPR (HA) did not participate in the voting. For the second Delphi, modifications were made based on the feedback received on the first Delphi and all three statements passed the 85.0% minimal approval rate. All statements approved on the Delphi process were presented in the meeting for audience voting and validation statement regarding the absence of contraindications to MIPR in high-risk patients had an 82.0% audience approval but was excluded by the Validation Committee as it was redundant. The expert and audience approvals, as well as quality scores provided by the Validation Committee, varied among PICO and Non-PICO questions (Supplementary Figure S1, <http://links.lww.com/SLA/B781>). Experts' approval for all the statements after the second Delphi was 97.5% (85.0–100.0, median and range), the audience agreement was 94.3% (51.1–100.0), and quality scores by the Validation Committee were 75.0% (29.0–90.0). Despite high expert and audience approval rates, and high-quality scores for left pancreatectomy [97.5% (85.0–100); 91.8% (82.0–100.0); 85.0% (82.0–90.0); respectively], quality scores for MIPD were low [95.0% (90.0–100.0); 91.6% (87.3–98.1); 41.0% (30.0–70.0)]. Non-PICO

questions followed the same trend of high expert and audience agreements, with a quality score of 70.0% [97.5% (87.5–100.0); 95.6% (51.1–100.0); 70.0% (29.0–82.0)].

The main purpose of the PICO questions (Q1–12) was to compare MIPR with OPR in aspects such as surgical outcomes, QoL, costs, and feasibility. When comparing MIDP with MIPD, MIDP has a greater number of studies, and the evidence level is higher, resulting in recommendations which are more clearly favoring MIPR. Nevertheless, despite good quality scores, there are still insufficient data on spleen preservation, best pancreatic stump closure methods, and central pancreatectomy, both for open and MIPR.

Three randomized studies have directly compared LPD and OPD, with contradicting results with respect to safety, and replicability. Two of these studies favoring LPD^{16,17} are limited by small numbers and by being from a single-institution/surgeon highly experienced in MIS. The one study showing negative result for LPD,¹⁵ appeared to be better designed, was multi-institutional and included a larger number of patients. However, the study was limited by the surgeons' experience on MIPD, as a surgeon was qualified to participate in the study after completing only 20 MIPDs. This seems to be reflected in the type of complications that led to the trend of increased mortality in the MIPD group, which resulted in early termination of the study.

During the process of developing the IG-MIPR guidelines, it became evident that in every perioperative phase of MIPR, both an opportunity and a need exist for further research. Preoperatively, there are gaps in the understanding which is the best comorbidity assessment to use for pancreatic surgery. An objective analysis of which parameters would better select patients and favor or contraindicate a particular approach, is needed.

Intraoperatively, there are very few studies addressing pre-emptive vascular control, timing, and reason for conversion. Good-quality, comparative studies on the best ways to address the pancreato-jejunostomy in MIPD and pancreas stump closure in MIDP are also lacking. Postoperatively, studies on QoL and analysis of costs are limited.

The need for data registries and formal training in MIPR was also repeatedly stressed during the meeting. Also, the definition of high- and low-volume centers and their role in MIPR needs to be improved. In the future, the combination of mandatory outcomes recording and formal MIPR training programs will likely lead to national hospital accreditation to MIPR. Based on the current evidence, it was recommended that centers should perform at least 20 MIPD per year to prevent increased morbidity as compared to OPD.

A main point of the meeting was emphasizing that MIPR has progressive levels of technical refinement that range from enucleations to highly complex surgeries with vascular resections. As such, it was agreed that centers should have a process for safe implementation of MIPR and participation in registries, which allow for future comparative studies. Evaluation of a particular procedure's benefit is better done in places that have already attained the learning curve for MIPR. Nevertheless, better studies are needed to assess what is, and how to address such a learning curve.

During the meeting, it was also stressed that similar standards should apply to open pancreas resections. Clear expert and audience agreement advocated that following outcomes and participation in registries should also be mandated for OPD.

With the recent rapid growth of MIPR, the Miami Guidelines provide up-to-date evidence as well as expert opinion. As technology advances, adoption increases, registries are expanded, and collaborative studies are produced, and there will be a need to revisit these guidelines in future years. Updates should be done using a strict methodology and fostering participation and partnership of a focused, but diverse group of international experts.

SUMMARY

The IG-MIPR effort illustrates a strong collaboration of multiple and diverse pancreas experts from around the world, bridging the domains of open, laparoscopic, and robotic surgery.

The Miami Guidelines are a starting point. As more and more studies are being done to increase the knowledge available in MIPR, better evidence will come to light on the differences in outcomes between open, laparoscopic, and robotic surgery, costs variance, QoL, the rationale for conversion, and best ways for training and implementation.

What is clear is that laparoscopic, robotic, and open pancreas resections each have a role. Future randomized trials and studies should focus on better understanding the specific utility and benefits of each approach and how technical advances can improve outcomes. The recommendations defined during the IG-MIPR Miami meeting should guide current pancreas surgeons and institutions on the role of MIPR in pancreatic surgery, foster its safe implementation, and guide future advances.

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