**The Miami International Evidence-Based Guidelines on Minimally Invasive Pancreas Resection (IG-MIPR)**

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**ABSTRACT**

**Objective** At the International Evidence-based Guidelines on Minimally Invasive Pancreas Resection (IG-MIPR) meeting in Miami, March 18-19 2019, the first evidence-based guidelines on MIPR were finalized and externally validated.

**Background** MIPR, comprising both laparoscopic and robotic pancreatic surgery, has seen a rapid development in the past decade. Initially, early adaptors from a few high-volume centers reported excellent outcomes of MIPR. Subsequently, several multicenter series as well as the first randomized controlled trials were published, and training programs were developed. These evidence-based guidelines identify best practices and aim to encourage patient safety as the use of MIPR is rapidly expanding around the world.

**Methods** The SIGN methodology was used, incorporating these four items: 1) systematic reviews using PubMed, Embase and Cochrane databases to answer clinical questions, whenever possible in PICO style, 2) the GRADE approach for assessment of the quality of evidence, 3) the Delphi method for establishing consensus on the developed recommendations and 4) the AGREE-II instrument for the assessment of guideline quality and external validation. The current guidelines are co-sponsored by IHPBA, AHPBA, A-PHPBA, E-AHPBA, EAES, Pancreas Club, SAGES, and SSAT.

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

**Conclusion*:*** These international evidence-based guidelines on MIPR using SIGN methodology give guidance to surgeons, hospital administrators, patients and medical societies on the use and outcome of MIPR and the approach to be taken regarding this challenging type of surgery.

**INTRODUCTION**

Minimally invasive pancreas resection (MIPR) comprises both, laparoscopic and robotic pancreatic surgery. MIPR has seen a rapid development in the past decade. Initially, early adaptors from a few high-volume centers performed these procedures and reported excellent outcomes.1–8 Thereafter, multicenter series9–13, and even the first (monocenter and multicenter) randomized controlled trials14–17 were published and training programs developed.18–20 However, evidence-based guidelines for this field are still lacking. Evidence-based guidelines do not claim to answer all relevant questions by studies of high level of evidence, but rather use SIGN, which incorporates the rigorous GRADE methodology to answer PICO-style questions, based on systematic reviews including both randomized and non-randomized studies, to provide recommendations accompanied by a score of the quality of evidence and strength of recommendations.

The first international consensus-based meeting on MIPR was organized in São Paulo, during the IHPBA 2016 meeting and was co-sponsored by the AHPBA. In the March issue of HPB 2017 several papers reported the outcome of this meeting.21

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 rather dig deeper into the available evidence. The current guideline is co-sponsored by multiple international surgical societies and contains evidence on both laparoscopic and robotic pancreatoduodenectomy, distal pancreatectomy, central pancreatectomy, patient selection, training, learning curve and minimal annual center volume in order to obtain optimal outcomes and patient safety.

**METHODS**

The present evidence-based guideline is a joint initiative of the International Hepato-Pancreato-Biliary Association (IHBPA), the Americas Hepato-Pancreato-Biliary Association (AHPBA), the Asian-Pacific Hepato-Pancreato-Biliary Assocation (A-PHPBA), 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), and the Society of the Alimentary (SSAT)and involves international experts (Appendix 1).

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 2-5 MD PhD students who performed the systematic literature reviews and 5-8 experts in the field (see Figure 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 method22 which incorporates the GRADE methodology.23

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

(a) *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 published in English, and available in full text. SIGN methodology22 was used to assess the quality of the evidence.

(b) *Summary of studies:*  A summary of each reviewed manuscript was completed and a brief summary of the literature along with evidence tables were created for each question, aggregating the studies in order to facilitate answering the questions.

(c) *Recommendations:* Recommendations were formulated based on the available evidence. All recommendations included a GRADE rating23 (see Table 1 and 2) based on 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 given to emphasize research opportunities to improve the quality of evidence.

Each group submitted the above listed items (a-d) per question to the steering committee prior to 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 (HA, MGB and MAH). 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 (HA) who did not participate in the Delphi vote. Recommendations were approved if an agreement rate of 85% or above 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 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. During the meeting two additional processes took place:

1. AGREE II: The validation committee used the AGREE II instrument24 (to assess the quality of the current guidelines).

2. 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 in order 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 committee prior to submitting the manuscript for publication.

**RESULTS**

The six main topics (A-F) are presented consecutively, incorporating 28 clinical questions (Q1-Q28) and their corresponding recommendations (see 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 Figure 3. The IG-MIPR meeting was attended by 117 surgeons from over 20 countries.

A. Distal and central pancreatectomy

**Q1. Should minimally invasive distal pancreatectomy (MIDP) versus open distal pancreatectomy (ODP) be used regardless of indication, when appropriate?**

Recommendation: Q1a) 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 (GRADE 1B, expert agreement 95%, quality score 85%, audience agreement 100%). 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%, audience agreement 91%). Q1c) MIDP is associated with a better postoperative quality of life (QoL) than ODP (GRADE 2B, expert agreement 85%, quality score 85%, audience agreement 88%).

Comments: One multicenter randomized controlled trial (RCT) comparing MIDP with ODP reported a shorter hospital stay and reduced blood loss after MIDP, while the overall complication rate was similar.14 Hereby confirming the findings of 10 systematic reviews and meta-analyses.25–34 Cost effectiveness of LDP compared to ODP was reported in two studies and showed a similar or slightly decreased total hospital cost after LDP.35,36 The RCT and one case-control study showed a higher quality of life (QOL) during the first 30 days following MIDP.14,37 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:. Design and participation in prospective trials evaluating cost and QOL outcomes.

**Q2. Should MIDP versus ODP be used for treatment of pancreatic ductal adenocarcinoma (PDAC)?**

Recommendation: MIDP for PDAC appears to be a feasible, safe and oncologically equivalent technique in experienced hands, although prospective comparative studies are lacking (GRADE 2B, expert agreement 95% , quality score 87%, audience agreement 96%).

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.29,38,39 One meta-analysis found a lower lymph node yield during MIDP39, while another meta-analysis found a similar lymph node yield in both approaches.29 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: Design and conduct additional randomized trials in order to increase the level of evidence.

**Q3. Should MIDP versus ODP be used for treatment of left sided pancreatic adenocarcinoma with vascular resection?**

Recommendation: There is no evidence 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%, audience agreement 98%).

Comments: No literature addressing this topic was identified.

Proposed action: Participation in retrospective and/or prospectively maintained database studies and registries.

**Q4a. Should staple versus another type of closure be used for stump closure in MIDP?**

Recommendation: Both stapler and non-stapler closure can be used in MIDP as outcomes are comparable (GRADE 1C, upgraded from 2C, expert agreement 100%, quality score 82%, audience agreement 86%).

Comments: Several studies reported the safety and feasibility of staple closure in single arm series40,41or non-comparative series between ODP and MIDP.42,43 Gradual compression stepwise closure should be encouraged.44

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%, audience agreement 82%).

Comments: Data supporting the use of staple line reinforcement specific for MIDP is 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.45,46 One retrospective study on MIDP found no differences in POPF rate between the group who received TachoSil® and those whom not received the surgical patch.47 Mesh reinforcement was suggested by one RCT to reduce the pancreatic fistula rate, but data on MIDP and OPD were not separated.48

Proposed action: Adding to the action plan on 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%, quality score 90%, audience agreement 98%).

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 laparoscopic distal pancreatectomy (LDP) versus robotic distal pancreatectomy (RDP) be used for 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%, quality score 83%, audience agreement 96%).

Comments: Four meta-analyses and one propensity score matched study suggested comparable surgical outcomes between laparoscopic and robotic distal pancreatectomy in terms of POPF rate49–53 and overall morbidity.49–51,54 Spleen-preservation rates might be higher during robotic pancreatectomy49,50,52 or at least similar.51,53 The oncological outcomes are not different between these modalities.50,55,56

Proposed action: Initiation of a randomized trial comparing LDP with RDP, 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 vs open central pancreatectomy are inadequate in quality and quantity (GRADE 1C upgraded from 2C, expert agreement 97.5%, quality score 84%, audience agreement 85%).

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.57 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% after laparoscopic central pancreatectomy.58

Proposed action: Prospective database studies and registries to improve the equality 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%, audience agreement 92%).

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.59,60 Open enucleation was mainly chosen for deep or posterior lesions61, larger or multiple tumors62 or expected malignancy. 62,63

Proposed action: Prospective database studies and registries to improve the level of evidence on this topic.

B. Pancreatoduodenectomy

**Q8. Should minimally invasive pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy (OPD) be used regardless of indication, when appropriate?**

Recommendation. 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 databases (GRADE 2A, expert agreement 90%, quality score 39%, audience agreement 92%).

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 one multicenter RCT showed no difference in outcomes but was prematurely stopped due to safety concerns as a results of a higher 90-day mortality in the LPD group (P=0.2).15 In this trial, the major complication (Clavien-Dindo 3 or above) rate was comparable between the two 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.5,6,12,13,15–17,64–103 Literature suggests MIPD should be limited to experienced surgeons in high volume centers due to the long learning curve and the difficulty of the procedure.5,13,79,93,94,101

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 treatment of periampullary 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%, audience agreement 91%).

Comments: Oncological outcomes appear similar for the two approaches.67,69,78,87,88,93 No difference has been observed in overall survival, 30-day and 90-day mortality.67,73,84 In one series, the progression free survival was reported to be longer in MIPD.67

Proposed action: As per Q8.

**Q10. Should MIPD versus OPD be used for 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%, quality score 30%, audience agreement 87%).

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 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%, quality score 41%, audience agreement 93%)

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.68

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 laparoscopic pancreatoduodenectomy (LPD) versus robotic pancreatoduodenectomy (RPD) be used for 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%, quality score 70%, audience agreement 98%).

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.80,104–107

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.

C. Patients and Technique

**Q13. Are there contraindications for MIPR, connected with patient age, obesity, or complex prior abdominal operations?**

Recommendation: There are no contraindications for MIPR based on patient age, obesity or prior abdominal surgery. (GRADE 1C, upgraded from 2C, expert agreement 97.5%, quality score 70%, audience agreement 98%)

Remark:visceral obesity and major abdominal surgery increase operative time, surgical difficulty and conversion rate. Relative contraindications do exist based on surgeon experience, comfort, center volume and experience and intraoperative findings (e.g. 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: Looking at elderly patients, outcomes between MIPR and the open approaches are comparable.92,99,108–110 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.111 When comparing RPD vs OPD in obese patients, those undergoing RPD showed to have a shorter operative time, less estimated blood loss (EBL) and a lower POPF rate.72 In a case matched study comparing patients with previous upper abdominal surgery to patients without such previous surgery, no differences were found.112

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%, audience agreement 75%)

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, less complications, and a shorter hospital stay compared with high-risk ODP (n=32).112

Proposed action: Centers with prospectively maintained databases could 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%, audience agreement 89%)

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%, audience agreement 100%).

Comments: Risk factors associated with an increased conversion rate are smoking, elevated BMI, surgeon case experience and malignancy.113–118 No studies specifically assessed the timing of conversion.

Proposed action: Authors are encouraged to record reasons for conversion, elective/pre-emptive versus urgent, and timing of conversion.

D. 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%, audience agreement 95%).

Comments: Training programs for MIDP18, LPD19 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 (1) a virtual reality simulation, (2) a biotissue curriculum, (3) a video library training, (4) intraoperative evaluation, and (5) skill maintenance with ongoing assessment.20 The evaluation of the RPD training program showed that fellows increasingly performed a complete procedure.119 The first two steps of the RPD training program are reported separately; step one is a virtual reality robotic simulation curriculum120 and step two a biotissue drill on the robot simulating steps of PD.121 Both show improvement of outcomes after completing that step.

Proposed action: HPB training programs should specify if 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%, quality score 77%, audience agreement 96%).

Comments: Depending on the outcome that was used to assess the learning curve, 10-40 cases have been described to be required to reach proficiency in LDP.58,122–128 For RDP the number of cases described is 7-37.123,129,130 In LPD learning curve related improvements in outcome were seen after 10-50 cases.58,131–134 For RPD 20-40 cases have been described as needed to overcome the learning curve.103,130,135,136 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 source 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 two-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%, audience agreement 98%).

Comments: No evidence exists on a two surgeon approach in MIPR. A study comparing outcomes of LDP performed by expert surgeons and surgeons in training, reports comparable outcomes.137

Proposed action: Centers performing MIPR are recommended to participate in prospective registries and include this data point.

**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 (centers performing <10 MIPD/year) and morbidity (centers performing <20 MIPD/year) are worse when performed in a low volume setting (GRADE 1B, expert agreement 97.5%, quality score 82%, audience agreement 85%).

Comments: Center volume is associated with morbidity94,138and mortality93,101,139 when looking at total PD93,94,139 and MIPD volume.101,138 A decreased complication rate was seen in centers performing >20 MIPD/year138 or >20 total PD/year.94 Mortality rates decreased from an annual volume of >10 total PD or MIPD.93,101,139

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: 1) implementation of dedicated individual and team training, 2) having >1 surgeon performing MIPR at the institution, 3) monitoring outcomes of MIPR for quality assurance, 4) consideration of surgeon/institution volume of pancreas resections including MIPR (GRADE 2C, upgraded from EXPERT OPINION, expert agreement 97.5%, quality score 75%, audience agreement 93%)

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.

E. Instrumentation

**Q22. Are there safety advantages 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%, quality score 51%, audience agreement 96%).

Comments: No literature addressing this topic was identified. Each surgeon should use the energy device they favor and are more familiarized with.

**Q23. Is there a need 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%, audience agreement 89%).

Comments: Two studies were found regarding the use of augmented reality in pancreatic surgery, concluding that it might increase surgical efficacy.140,141

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

F. 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%, quality score 82%, audience agreement 100%).

Comments: No literature addressing this topic was identified.

**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%, quality score 82%, audience agreement 98%).

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 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%, audience agreement 100%).

Comments: No literature addressing this topic was identified.

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

**DISCUSSION**

MIPR has seen a rapid development over the past decade and outcomes, particularly for MIPD, have varied significantly. Despite of experienced centers showing 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.

It would be unrealistic to expect that 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 unbiassed assessment and appropriate dissemination of MIPR. These guidelines also underline areas in which further research and development is needed.

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

The International Evidence-Based Guidelines on Minimally Invasive Pancreas Resection 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 are being endorsed by eight 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 over 20 countries.

During the first Delphi, only three 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 on 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% minimal approval rate. All statements approved on the Delphi process were presented in the meeting for audience voting and validation committee reevaluation.

The validation 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 6 ½ hours­ throughout the meeting, using the AGREE methodology for each guideline statement.

One statement, regarding equipment received a low approval by the audience (51%) and was likewise voted for exclusion by the Validation Committee (quality score of 29%). Another statement regarding the absence of contraindications to MIPR in high risk patients had an 82% audience approval but was excluded by the Validation Committee.   
The experts and audience approvals, as well as quality scores provided by the Validation Committee varied among PICO and Non-PICO questions (see figure 3). Experts’ approval for all the statements after the second Delphi was97.5% (85 – 100, median and range), the audience agreement was 94.3% (51.1 – 100) and quality scores by the Validation Committee 75% (29 - 90). Despite high expert and audience approval rates, and high quality scores for left pancreatectomy (97.5% (85 – 100); 91.8% (82 – 100); 85% (82 – 90); respectively), quality scores for Whipple procedure was low (95% (90 - 100); 91.6% (87.3 - 98.1); 41% (30 - 70)). Non-PICO questions followed the same trend of high expert and audience agreements, with a quality score of 70% (97.5 (87.5 - 100); 95.6 (51.1 - 100); 70 (29 - 82)).

The main purpose of the PICO questions (Q1-12) was to compare MIPR with OPR in aspects such as surgical outcomes, quality of life, 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 is still insufficient data on spleen preservation and central pancreatectomy, both for open and MIPR.

Three randomized studies have directly compared LPD and OPD, with contradicting results in regard to safety, and replicability. Two of them favoring LPD16,17 are limited by small numbers and by being from a single institution/surgeon highly experienced in MIS. The one study against LPD15 appeared to be better designed, was multi-institutional and included a larger number of patients. However, the study was limited by the experience of surgeons performing MIPD, a surgeon could participate after completing only 20 MIPD. This seems to be reflected by the type of complications that lead 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 there is both opportunity and need for further research. Preoperatively, there are gaps in the understanding of which is the best comorbidity index to use for pancreatic surgery, as well as an objective analysis of which parameters would clearly contraindicated MIPRs. Intraoperatively, there are very few studies addressing preemptive 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 quality of life and analysis of costs are limited.

The need for data registries and formal training in MIPR were also repeatedly stressed during the meeting. There is a necessity to improve the definition of high and low volume centers and their role in MIPR. 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 in order to prevent increased morbidity as compared to OPD.

A main point of the meeting was underscoring 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 participate in registries which will 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 learning curve.

During the meeting it was also stressed that similar standards should apply to open pancreas resections. There was clear expert and audience agreement 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, there will be a need to review these guidelines in future years. This 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, crossing the barriers 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 into light on the differences in outcomes between open, laparoscopic and robotic surgery, costs variance, quality of life, rationale for conversion and best ways for training and implementation.

What is clear, is that laparoscopic, robotic and open pancreas resections have a role. Future randomized trials and studies should also focus on better understanding the utility and benefits of each approach. 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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**TABLES**

**Table 1.** GRADE recommendations. Adapted with permission from: Grading Tutorial. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on May 1st, 2019.) Copyright © 2019 UpToDate, Inc. For more information visit www.uptodate.com.

|  |  |  |
| --- | --- | --- |
| **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 |

**Table 2.** Quality of evidence in GRADE. Adapted with permission from: Grading Tutorial. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on May 1st, 2019.) Copyright © 2019 UpToDate, Inc. For more information visit www.uptodate.com.

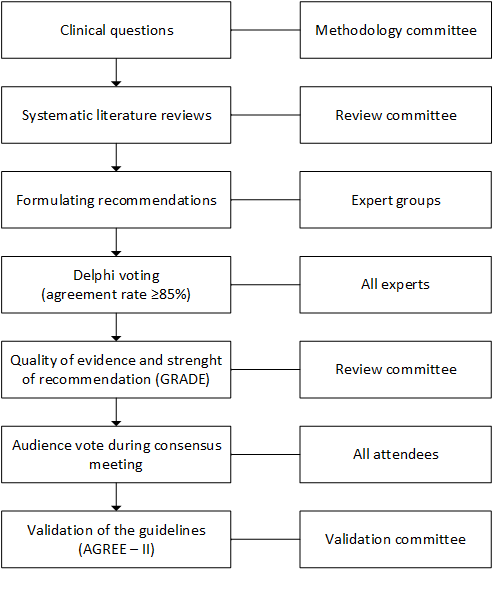
|  |  |
| --- | --- |
| A. High quality of evidence | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. |
| B. Moderate quality of evidence | Evidence 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. |

**Table 3.** Summary of recommendations

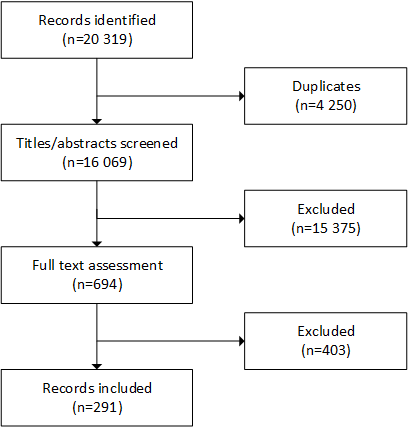
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| --- | --- | --- |
| 1. **Distal and central pancreatectomy** | | **GRADE** |
| 1a | Minimally invasive distal pancreatectomy (MIDP) for benign and low-grade malignant tumors is to be considered over open distal pancreatectomy (ODP) since it is associated with a shorter hospital stay, reduced blood loss and equivalent complication rates. | 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 (PDAC) 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 non-stapler 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 MI vs 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 |
| 1. **Pancreatoduodenectomy** | | |
| 8 | There is insufficient data to recommend minimally invasive (MIPD) over open pancreatoduodenectomy (OPD). Centers performing MIPD should be including all their MIPD outcomes data into national and international registries, and prospectively maintained pancreas database. | 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 exists 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 laparoscopic (LPD) and robotic pancreatoduodenectomy (RPD) exists. Surgeon training, experience and available resources currently guide which approach is utilized. | 2C |
| 1. **Patients and technique** | | |
| 13 | There are no contraindications for MIPR based on patient age, obesity or prior abdominal surgery. | 1C |
| 14 | The evidence to suggest a relationship between comorbidity and the outcome of minimally invasive pancreatic resection (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 |
| 1. **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: 1) implementation of dedicated individual and team training, 2) having >1 surgeon performing MIPR at the Institution, 3) monitoring outcomes of MIPR for quality assurance, 4) consideration of surgeon/institution volume of pancreas resections including MIPR | 2C |
| 1. **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 |
| 1. **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 HPB 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 |

**FIGURES**

**Figure 1.** Flow-chart of the guideline process.



**Figure 2.** Flow-chart of systematic literature review.



**Figure 3.** Boxplots of the experts and audience approval rates, and of the quality scores provided by the Validation Committee, sub-grouped by PICO and Non-PICO questions.

The boxes represent the interquartile range (IQR), lower quartile: dark gray (Q1); upper quartile: light gray (Q3); and median (M). The error bars represent the range.

3a. PICO questions – Left Pancreatectomy

3b. PICO questions - pancreatoduodenectomy

3c.Non-PICO questions

3d. All questions

**Appendix 1**

A. Steering committee

|  |  |
| --- | --- |
| **Name** | **Country** |
| Horacio J. Asbun - *Chair* | United States of America |
| Mohammed Abu Hilal - *Co chair* | United Kingdom |
| Marc Besselink - *Co chair* | The Netherlands |
| Michael Kendrick - *Co chair* | United States of America |
| Herbert Zeh *- Co chair* | United States of America |
| Adnan Alseidi | United States of America |
| Song-Cheol Kim | Korea |
| Barish Edil | United States of America |
| Melissa Hogg | United States of America |
| David Kooby | United States of America |
| Igor Khatkov | Russia |
| Yiping Mou | China |
| Masafumi Nakamura | Japan |
| Chinnusamy Palanivelu | India |
| Shailesh Shrikhande | India |
| Mathew Walsh | United States of America |

B. Methodology committee

|  |  |
| --- | --- |
| **Name** | **Country** |
| Horacio J. Asbun | United States of America |
| Mohammed Abu Hilal | United Kingdom |
| Marc Besselink | The Netherlands |
| Adnan Alseidi | United States of America |

C. Review committee

|  |  |
| --- | --- |
| **Name** | **Country** |
| Horacio J. Asbun - *Supervisor* | United States of America |
| Mohammed Abu Hilal - *Supervisor* | United Kingdom |
| Marc Besselink - *Supervisor* | The Netherlands |
| Alma Moekotte - *Co chair reviewers* | United Kingdom |
| Frederique Vissers - *Co chair reviewers* | The Netherlands |
| Alberto Balduzzi | Italy |
| Alessandro Coppola | Italy |
| Francisco de Leon | Spain |
| Caitlan Hester | United States of America |
| Maarten Korrel | The Netherlands |
| Nuria Lluis | Spain |
| Sanne Lof | United Kingdom |
| Arab Rawashdeh | United Kingdom |
| Dominic Sanford | United States of America |
| Nicky van der Heijde | United Kingdom |
| Jony van Hilst | The Netherlands |
| Maurice Zwart | The Netherlands |

D. Validation committee

|  |  |
| --- | --- |
| **Name** | **Country** |
| Kevin Conlon - *Chair* | Ireland |
| Federica Cipriani - *Facilitator* | Italy |
| Andrew Cook - *Methodologist* | United Kingdom |
| Claudio Bassi | Italy |
| Mark Callery | United States of America |
| Nicolas DeMartines | Switzerland |
| Cassidie Moravek | United States of America |
| Christos Dervenis | Greece |
| Pier Giulianotti | United States of America |
| Ho-Seong Han | Korea |
| Norihiro Kokudo | Japan |
| Quintus Molenaar | The Netherlands |
| William Nealon | United States of America |
| Henry Pitt | United States of America |
| John Primrose | United Kingdom |
| Kyoichi Takaori | Japan |
| Go Wakabayashi | Japan |
| Michael Zinner | United States of America |

E. Expert committee

|  |  |
| --- | --- |
| **Name** | **Country** |
| Bergthor Björnsson | Sweden |
| Ugo Boggi | Italy |
| Felipe Coimbra | Brazil |
| Claudius Conrad | United States of America |
| Michael D’Angelica | United States of America |
| Marco Del Chiaro | United States of America |
| Safi Dokmak | France |
| Bjørn Edwin | Norway |
| Paul Hansson | United States of America |
| Nicolas Jarufe | Chile |
| Rohan Jeyarajah | United States of America |
| Tobias Keck | Germany |
| Igor Khatkov | Russia |
| David Kooby | United States of America |
| Marcel Machado | Brazil |
| John Martinie | United States of America |
| Nipun Merchant | United States of America |
| Chinnusamy Palanivelu | India |
| Patrick Pessaux | France |
| Patricio Polanco | United States of America |
| Palanisamy Senthilnathan | India |
| John Stauffer | United States of America |
| Mark Talamonti | United States of America |
| Chung-Ngai Tang | China |
| Charles Vollmer | United States of America |
| Christopher Wolfgang | United States of America |
| Shin-E Wang | Taiwan |
| Amer Zureikat | United States of America |