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Invited Article

Korean Surgical Practice Guideline for Pancreatic Cancer 2022: A summary of evidence-based surgical approaches

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Pancreatic cancer is the eighth most common cancer and the fifth most common cause of cancer-related deaths in Korea. Despite the increasing incidence and high mortality rate of pancreatic cancer, there are no appropriate surgical practice guidelines for the current domestic medical situation. To enable standardization of management and facilitate improvements in surgical outcome, a total of 10 pancreatic surgical experts who are members of Korean Association of Hepato-Biliary-Pancreatic Surgery have developed new recommendations that integrate the most up-to-date, evidence-based research findings and expert opinions. This is an English version of the Korean Surgical Practice Guideline for Pancreatic Cancer 2022. This guideline includes 13 surgical questions and 15 statements. Due to the lack of high-level evidence, strong recommendation is almost impossible. However, we believe that this guideline will help surgeons understand the current status of evidence and suggest what to investigate further to establish more solid recommendations in the future.

Key Words: Pancreatic carcinoma; Surgery; Practice guideline

INTRODUCTION

Pancreatic cancer is the eighth most common cancer (with an annual new case number of approximately 7,000 in 2017) and the fifth most common cause of cancer-related death in South Korea [1]. The incidence and mortality of pancreatic cancer have increased gradually with a 5-year relative survival rate of 12.2% in 2017 with nearly no improvements in this figured over the last 20 years.

Despite the increasing incidence and high mortality rate of pancreatic cancer, there are no appropriate surgical practice guidelines for the current domestic medical situation regarding this cancer. Various practice guidelines for pancreatic cancer

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have been established and reported [2-4]. However, none of them has provided detailed guidelines for surgical procedures. Although Korean Clinical Practice Guidelines for Pancreatic Cancer 2021 has been published, only a limited number of surgical issues have been addressed [5]. Thus, surgeons in the committee of the Korean Clinical Practice Guideline for Pancreatic Cancer 2021 gathered and tried to establish a surgical practice guideline.

This guideline was designed to provide adequate surgical information and stimulate research to build evidence for the treatment of pancreatic cancer including 13 surgical questions and 15 statements. Among these 13 questions, four questions were extracted from the Korean clinical practice guidelines for pancreatic cancer 2021 with the addition of a few new references [5]. It is very difficult to obtain high-level evidence for the management of pancreatic disease, especially surgical management of pancreatic cancer. The low number of cases is insufficient to undertake a randomized controlled trial (RCT). The technique is too complicated to be standardized. In addition, technical issues are rapidly changing and supportive groups for clinical studies about surgery are rare. High-level evidence and strong recommendations are almost impossible. However, we believe that this guideline will help surgeons understand the current status of evidences and suggest direction for further studies to establish more solid recommendations.

GUIDELINE DEVELOPMENT METHODOLOGY

This surgical guideline primarily targets adult patients with suspected or newly diagnosed pancreatic ductal adenocarcinoma. This guideline is intended to provide useful surgical information and directions for all surgeons. It was developed by members of the Korean Association of Hepato-Biliary-Pancreatic Surgery. To complete this guideline, we established a development working group and a review panel for Korean Surgical Practice Guideline for Pancreatic Cancer 2022.

The process of new guideline development was as follows: (1) selecting clinical key questions (KQs), (2) determining development methods, (3) performing literature search and selection, (4) assessing the quality of the selected literature and synthesizing evidence, (5) determining the levels of evidence and strength of recommendations, and (6) providing statements for clinical questions.

Clinical KQs were specified by considering the population, intervention/index test, comparator, and outcome (PICO) elements. This guideline is the first Korean surgical practice guideline for pancreatic cancer. It was developed by *de novo* methods.

We systematically searched published literature using databases including Medline, Embase, Cochrane Library, and KoreaMed through May 2021. For the adaptation method, additional databases including the Guideline International Network and Korean Clinical Practice Guideline Information Center were searched. Manual searches were also performed to complement and update the results. Inclusion and exclusion criteria were determined by panels composed of pairs of clinical experts. These inclusion and exclusion criteria were predefined and tailored to KQs. Articles were screened by title and abstract. Full texts were then retrieved for selection. In each step, two panels performed selections independently. Agreements were reached.

We critically appraised the quality of selected studies using

Table 1. Levels of evidence

Level	Explanation
High	Study design (Intervention) Results from randomized controlled trials or comparative designed observational studies. (Diagnosis) Results from randomized controlled trials or diagnostic accuracy tests with a cross-sectional cohort design. Considerations: There are no concerns regarding the methodological assessment or the consistency or precision of the results. The certainty of evidence ishigh for the synthesized result.
Moderate	Study design (Intervention) Results from randomized controlled trials or comparative designed observational studies. (Diagnosis) Results from randomized controlled trials or diagnostic accuracy tests with a cross-sectional cohort design. Considerations: There are minor concerns regarding the methodological assessment or the consistency or precision of the results. The certainty of evidenceis moderate for the synthesized result.
Low	Study design (Intervention) Results from observational studies with or without comparison groups. (Diagnosis) Results from diagnostic accuracy tests with a case-controlled design. Considerations: There are serious concerns regarding the methodological assessment or the consistency or precision of the results. The certainty of evidence is low for the synthesized result.
Very low	Study design (Intervention) Results from observational studies without comparison groups or experts' opinions. (Diagnosis) Results from diagnostic accuracy tests with a case-controlled design. Considerations: There are very serious concerns regarding the methodological assessment or the consistency or precision of the results. The certainty of evidence is very low for the synthesized result.

risk-of-bias tools. We used Cochrane risk of bias (ROB) for RCTs, risk of bias for nonrandomized studies (RoBANS), and a measurement tool to assess systematic reviews (AMSTAR) for systematic reviews/meta-analyses [6-9]. Disagreements were resolved by discussion and seeking the opinion of a third member. We extracted data using a predefined format and synthesized the data qualitatively or quantitatively. Evidence tables were summarized according to KQs. In the adaptation method, we assessed the quality using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument for evaluating the currency, acceptability, and applicability of medical guidelines [10,11].

Levels of evidence and grading of recommendations were modified based on the Scottish Intercollegiate Guidelines Network (SIGN) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology reviews [12,13]. The evidence was classified into four levels (Table 1). Main factors were the study design and quality. In addition, we considered outcome consistency. The grading of recommendations was performed according to the modified GRADE methodology. It had four levels (Table 2). Recommendation factors considered were evidence level, balance of benefit and harm, and clinical applicability (resource and cost). The Development Working Group reviewed the draft and discussed the consensus. The Review Panel examined the final version of the draft through careful expert review. The guideline developed through this process was then endorsed by an open meeting of the Korean Pancreas Surgery Club. Revisions were made in accordance with suggestions at the open meeting. This guideline will be revised every five years when there is solid evidence that can affect outcomes of patients with pancreatic cancer.

RECOMMENDATIONS (Table 3)

Staging laparoscopy

KQ 1: Is staging laparoscopy routinely indicated in resectable pancreatic cancer (RPC)?

Recommendation 1: Staging laparoscopy could be considered selectively before laparotomy in patients with RPC

(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments: In retrospective cohort studies, diagnostic laparoscopy was effective in terms of decreasing cost and reducing unnecessary laparotomy by detecting occult metastases [14-18]. In addition, patients with staging laparoscopy received chemotherapy earlier than those with occult metastasis found during laparotomy, leading to improved survival [14,19]. However, the false-negative rate of staging laparoscopy was higher than that of exploratory laparotomy [15]. Therefore, careful observation is required during staging laparoscopy. According to a meta-analysis, staging laparoscopy could detect occult metastases not found in preoperative images in 14%–38% of patients with RPCs and 36% of those with locally advanced pancreatic cancer (LAPC) [20].

With improvement in preoperative imaging examinations such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), selective staging laparoscopy has been suggested [21,22]. However, evidence for the potential criteria for selective staging laparoscopy is still limited. A well-designed prospective multicenter randomized study on the effectiveness of staging laparoscopy is needed.

Table 2. Grading of recommendations

Strength of recommendations	Explanation
Strong recommendation	The intervention/diagnostic test can be strongly recommended in most clinical practice, considering greater benefit than harm, evidence level, value and preference, and resources.
Conditional recommendation	The intervention/diagnostic test can be conditionally recommended in clinical practice considering the balance of benefit and harm, evidence level, value and preference, and resources.
Not recommended	The harm caused by the intervention/diagnostic test may be greater than its benefits. Moreover, considering the evidence level, value and preference, and resources, the intervention should not be recommended.
Inconclusive	It is not possible to determine the strength and direction of recommendation because of a very low or insufficient evidence level, uncertain or variable balance of benefit and harm, value and preference, and resources.

Table 3. Summary of key questions and recommendations

Key question and recommendation	Strength of recommendation	Level of evidence
KQ 1. Is staging laparoscopy routinely indicated in resectable pancreatic cancer (RPC)? Recommendations: Staging laparoscopy could be considered selectively before laparotomy in patients with RPC.	Conditional	Low
KQ 2. Is minimally invasive surgery (MIS) applicable to the patients with RPC? Recommendations: MIS could be performed selectively for the patients with RPC by highly experienced surgeons.	Conditional	Low
KQ 3. Is extended lymph node dissection (LND) and nerve plexus dissection necessary during pancreaticoduodenectomy (PD) for the patients with resectable pancreatic head cancer (RPHC)? Recommendations: Extended LND is not recommended for the patients with RPHC.	Not recommend	High
KQ 4-1. Is combined portal vein (PV) or superior mesenteric vein (SMV) resection beneficial in patients with pancreatic cancer invading the PV or SMV? Recommendations: PV or SMV resection could be considered if radical resection is possible in patients with pancreatic cancer invading the PV or SMV.	Conditional	Low
KQ 4-2. Is superior mesenteric artery (SMA) resection beneficial in patients with pancreatic cancer invading the SMA? Recommendations: SMA resection is not recommended in patients with pancreatic cancer invading the SMA.	Not recommend	Low
KQ 4-3. Is distal pancreatectomy with celiac axis resection (DP-CAR) beneficial in patients with pancreatic cancer invading the celiac axis (CA)? Recommendations: DP-CAR could be considered, if radical resection is possible in patients with pancreatic cancer invading the CA.	Conditional	Low
KQ 5. Is mesopancreas excision (MpE) beneficial during PD? Recommendations: MpE could be considered to improve the rate of R0 resection for the patients with RPHC	Conditional	Low
KQ 6. Is pylorus preserving pancreaticoduodenectomy (PPPD) preferred to PD in RPHC? Recommendations: PPPD is preferred to PD in RPHC.	Conditional	High
KQ 7. Is additional pancreas resection necessary in cases of positive pancreatic resection margin in intraoperative frozen biopsy? Recommendations: Additional pancreas resection could be considered if pancreatic resection margin is positive in intraoperative frozen biopsy.	Conditional	Low
KQ 8. Is radical antegrade modular pancreatosplenectomy (RAMPS) beneficial in pancreatic body or tail cancer? Recommendations: RAMS could be considered in pancreatic body or tail cancer.	Conditional	Low
KQ 9. Is bypass gastrojejunostomy necessary in cases of unresectable pancreatic cancer without gastric outlet obstruction? Recommendations: Bypass gastrojejunostomy is not recommended in patients with unresectable pancreatic cancer without gastric outlet obstruction.	Not recommend	Low
KQ 10. Is pancreatectomy beneficial in cases of pancreatic cancer with pathologically proven para-aortic lymph node metastasis in intraoperative frozen biopsy? Recommendations: Recommendation to perform pancreatectomy in cases of pancreatic cancer with pathologically proven para-aortic lymph node metastasis in intraoperative frozen biopsy is withheld.	Inconclusive	Very low
KQ 11. Is hepatic resection beneficial in cases of pancreatic cancer with hepatic oligometastasis? Recommendations: Recommendation to perform hepatic resection in cases of pancreatic cancer with hepatic oligometastasis is withheld.	Inconclusive	Very low
KQ 12. Is conversion surgery beneficial in cases of locally advanced pancreatic cancer (LAPC)? Recommendations: Conversion surgery after induction chemotherapy could be considered in cases of LAPC.	Conditional	Low
KQ13. Is artery first approach in pancreaticoduodenectomy (AFA-PD) beneficial in cases of pancreatic head cancer? Recommendations: Recommendation to perform AFA-PD in cases of pancreatic head cancer is withheld.	Inconclusive	Very low

Minimally invasive surgery (MIS)

KQ 2: Is MIS applicable to patients with RPC?

Recommendation 2: MIS could be performed selectively for patients with RPC by highly experienced surgeons
(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments:

1) Pancreaticoduodenectomy (PD)

There was no difference in postoperative complication rate between MIS and open surgery for PD [23-28]. Their reported 30-day mortality rates were also similar [24-29]. Median survival durations after MIS and open surgery of PD were comparable in six studies [23-28]. Zhou et al. [28] have reported better survival in open surgery. However, this difference did not persist after propensity-score matching (Table 4) [28]. Four meta-analyses have found no differences in complications, mortality, or survival between MIS and open surgery for PD [30-33]. However, selection bias requires cautious interpretation of these findings.

Table 4. Summary of retrospective cohort studies of pancreaticoduodenectomy

Author	Comparison group	Number	Morbidity rate (%)	*p*-value	30-day mortality (%)	*p*-value	Median survival (mon)	*p*-value
Adam et al. (2015) [29]	Laparoscopy/robot	831	N/A	-	42 (5.1)	0.10	N/A	-
	Open	5,235			199 (3.8)			
Choi et al. (2020) [23]	Laparoscopy	27	10 (37.0)[a]	0.700	N/A		44.62	0.223
	Open	34	10 (29.4)				45.29	
Croome et al. (2014) [24]	Laparoscopy	108	6 (5.6)	0.17	1 (0.9)	0.50	25.3	0.12
	Open	214	29 (13.6)		4 (1.9)		21.8	
Girgis et al. (2021) [25]	Robot	163	40 (24.5)	0.265	3 (1.8)	1.00	25.6[b]	0.055
	Open	198	59 (29.8)		3 (1.5)		23.9[b]	
Kuesters et al. (2018) [26]	Laparoscopy	62	25 (40.3)	0.81	3 (4.8)	0.23	20%[c]	0.51
	Open	278	107 (38.5)		6 (2.2)		14%[c]	
Stauffer et al. (2017) [27]	Laparoscopy	58	13 (22.4)	0.170	2 (3.4)	N/A	18.5	0.25
	Open	193	58 (30.1)		10 (5.2)		30.3	
Zhou et al. (2019) [28]	Laparoscopy	79	9 (11.4)	0.333	1 (1.3)	> 0.999	18.0	0.032
	Open	230	18 (7.8)		2 (0.9)		22.8	(0.293)[d]

N/A, not available.
[a]Postoperative pancreatic fistula; [b]includes distal pancreatectomies; [c]5-year survival rate; [d]after propensity score matching analysis.

2) Distal pancreatectomy (DP)

Five studies have reported comparable or better complication rates and postoperative mortality rates of MIS versus open surgery for DP [25,34-37]. Long-term survival rates were comparable between MIS and open surgery for DP [25,36-39]. Survival benefit of MIS has been demonstrated in two studies (Table 5) [34,35]. In one meta-analysis, there were no differences in complication rates, severe complication rates, postoperative mortality rates, or long-term survival rates between MIS and open surgery for DP [40].

MIS PD and has comparable short- and long-term outcomes with open surgery and has the advantage of reducing pain, blood transfusion, and hospital stay. In particular, faster recovery after MIS may be a significant advantage for patients who require postoperative adjuvant treatment. However, since MIS is a complex and difficult surgical procedure, radical resection of the tumor and patient safety might not be guaranteed when this procedure is performed by under-experienced surgeons.

Although the literature indicated comparable or better results of MIS versus open surgery in terms of postoperative morbidity and mortality as well as long-term survival, these findings were derived from retrospective data with possible se-

Table 5. Summary of retrospective cohort studies of distal pancreatectomy

Author	Comparison group	Number	Morbidity rate (%)	*p*-value	90-day mortality (%)	*p*-value	Median survival (mon)	*p*-value
Anderson et al. (2017) [38]	Laparoscopy/robot	505	N/A	-	11 (2.2)	0.10	55%[a]	0.42
	Open	1,302			43 (3.3)		52%[a]	
Girgis et al. (2021) [25]	Robot	48	8 (16.7)	0.724	3 (6.25)	1.00	25.6[b]	0.055
	Open	25	5 (20.0)		1 (4.0)		23.9[b]	
Kantor et al. (2017) [39]	Laparoscopy	349	N/A	-	9 (3.7)	0.26	29.9	0.09
	Open	1,205			52 (5.6)		24.0	
Lee et al. (2014) [34]	Laparoscopy/robot	12	3 (25.0)	0.412	0 (0)[c]	0.484	60.0	0.046
	Open	78	29 (37.2)		2 (2.6)[c]		30.7	
Sulpice et al. (2015) [35]	Laparoscopy	347	23 (6.6)	0.0284	9 (2.6)	0.0215	62.5	< 0.0001
	Open	2,406	251 (10.4)		135 (5.6)		36.7	
van Hilst et al. (2019) [36]	Laparoscopy/robot	340	61 (17.9)	0.431	7 (2.1)	> 0.999	28	0.774
	Open	340	70 (20.6)		8 (2.4)		31	
Zhang et al. (2015) [37]	Laparoscopy	17	6 (35.3)	0.754	0 (0)	N/A	14.0	0.802
	Open	34	14 (41.2)		1 (2.9)		14.0	

N/A, not available.
[a]Three-year overall survival; [b]includes pancreatoduodenectomy; [c]postoperative within 30-day mortality.

lection bias. Therefore, the evidence for MIS remains low and MIS cannot be strongly recommended in general. MIS may be performed for well-selected patients with pancreatic cancer by highly experienced expert surgeons in MIS.

Extended lymph node dissection (LND)

KQ 3: Is extended LND and nerve plexus dissection necessary during PD for patients with resectable pancreatic head cancer (RPHC)?

Recommendation 3: Extended LND is not recommended for patients with RPHC

(Strength of recommendation: Not recommend;
Level of evidence: High)

Comments: Five RCTs have reported increased postoperative complication and mortality rates after extended LND, albeit not statistically significant [41-45]. Moreover, extended LND did not result in improved survival outcomes. It even led to worse survival outcomes in some studies (Table 6) [43,44,46]. Three meta-analyses also demonstrated that extended LND did not have survival gain [46-48]. Two studies confirmed higher postoperative complication and mortality rates after extended LND, although differences were not statistically significant [47,48].

Extended LND demands a longer operative time and surgeons' effort. It increases the risk of complications and mortality rate without offering any survival benefit. Therefore, an extended LND is not generally recommended. It may be performed in limited cases where widespread lymph node metastasis is highly suspected. However, unnecessary extended LND should be avoided by utilizing frozen biopsy of suspected lymph nodes in fields beyond the standard extent.

Vascular resection

KQ 4-1: Is combined portal vein (PV) or superior mesenteric vein (SMV) resection beneficial in patients with pancreatic cancer invading the PV or SMV?

Recommendation 4-1: PV or SMV resection could be considered if radical resection is possible in patients with pancreatic cancer invading the PV or SMV

(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments: Five meta-analyses have summarized findings for this question [49-53]. Patients who underwent PV/SMV resection tended to have a slightly higher postoperative mortality [49-51] and reoperation rate [49,50,52], lower curative resection rate and survival rate [49-52], longer operative time and hospital stay [49,50,52], and more complications such as pancreatic fistula, delayed gastric emptying, or bleeding than those who received standard pancreatectomy without PV/SMV resection [49,50,52]. Considering that more patients with advanced pancreatic cancer were included in the PV/SMV resection group, the survival rate in the PV/SMV resection group was similar to that in the non-PV/SMV resection group if R0 was achieved. In a study that included only the PV/SMV resection group, curatively resected patients showed better survival than non-curatively resected patients [52].

PV/SMV resection could be beneficial if performed by a highly skilled surgeon to obtain R0 resection and minimize mortality or postoperative complications.

Table 6. Summary of randomized controlled trials comparing extended lymph node dissection (LND) and standard LND

Author	Comparison group	Number	Morbidity rate (%)[a]	*p*-value	Postoperative mortality rate (%)	*p*-value	Survival rate (%)	*p*-value
Farnell et al. (2005) [41]	Extended	39	N/A	NS[a]	1 (2.6)	NS	17 (5-yr)	0.320
	Standard	40			0 (0)		16 (5-yr)	
Nimura et al. (2012) [42]	Extended	50	22.0	NS	1 (2.0)	NS	6.0 (5-yr)	0.119
	Standard	51	19.6		0 (0)		15.7 (5-yr)	
Jang et al. (2014) [43]	Extended	86	37 (43.0)	0.160	2 (2.3)	NS	35.7 (2-yr)	0.122
	Standard	83	27 (32.5)		0 (0)		44.5 (2-yr)	
Jang et al. (2017) [44]	Extended	86	N/A	-	N/A	-	14.4 (5-yr)	0.388
	Standard	83					18.4 (5-yr)	
Ignjatovic et al. (2017) [45]	Extended	30	1 (3.3)[b]	> 0.05	2 (6.7)	> 0.05	7.1 (5-yr)	0.057
	Standard	30	0 (0)		1 (3.3)		6.9 (5-yr)	

N/A, not available; NS, not significant.
[a]Complications were evaluated separately and not as a whole. There were no differences for all sub-specified complications. [b]Postoperative bleeding.

KQ 4-2: Is superior mesenteric artery (SMA) resection beneficial in patients with pancreatic cancer invading the SMA?

Recommendation 4-2: SMA resection is not recommended in patients with pancreatic cancer invading the SMA

(Strength of recommendation: Not recommend; Level of evidence: Low)

Comments: Since the SMA is surrounded by numerous lymph nodes and nerve plexuses, radical resection is technically more difficult than PV or SMV resection. Since all reviewed studies included heterogeneous patients who underwent PV, SMV, common hepatic artery, or SMA resection, it was difficult to select and analyze patients who underwent SMA resection [54-59]. Retrospective studies have demonstrated comparable survival rates in SMA resected patients to those in patients without SMA resection [54-56]. However, recently published meta-analyses have shown worse survival rates and higher rates of morbidity and mortality in the SMA resection group than in the non-SMA resection group [57-59]. Therefore, SMA resection should not be generally recommended. Although some surgeons may perform SMA resection in case of showing excellent response after neoadjuvant chemotherapy, further studies focusing on patients who undergo combined SMA resection after neoadjuvant chemotherapy are needed.

KQ 4-3: Is distal pancreatectomy with celiac axis resection (DP-CAR) beneficial in patients with pancreatic cancer invading the celiac axis (CA)?

Recommendation 4-3: DP-CAR could be considered if radical resection is possible in patients with pancreatic cancer invading the CA

(Strength of recommendation: Conditional; Level of evidence: Low)

Comments: DP-CAR is a challenging procedure. It has yielded certain clinical efficacy in the treatment of LAPC invading the CA. However, the clinical efficacy and safety of DP-CAR remain controversial. Median survival rate of DP-CAR group was 17.5–20 months. The survival rate of the DP-CAR group was comparable to that of the DP without CA resection group [60-66], but significantly higher than that of the non-pancreatectomy group [60,62,65]. In meta-analyses, the R0 resection rate of DP-CAR group was 72.8%. The postoperative complication rate of the DP-CAR group was significantly higher than that of the DP group while the hospital mortality rate was comparable [64,65].

DP-CAR is complicated procedure with a high morbidity rate. However, since DP-CAR showed better survival than the non-resected group, DP-CAR could be performed to improve the R0 resection rate and survival rate by highly skilled surgeons for carefully selected patients.

Mesopancreas excision (MpE)

KQ 5: Is MpE beneficial during PD?

Recommendation 5: MpE could be considered to improve the rate of R0 resection for patients with RPHC

(Strength of recommendation: Conditional; Level of evidence: Low)

Comments: Mesopancreas is defined as a firm and well-vascularized structure extending from the posterior surface of the pancreatic head to behind the mesenteric vessels. The concept of MpE in pancreatic head cancer (PHC) was proposed in analogy to the concept of total mesorectal excision for rectal cancer to better control locoregional recurrence by achieving a complete excision of the mesopancreas during PD and to increase R0 resection rate for PHC. In retrospective cohort studies, R0 resection rates of MpE were approximately 90%, significantly higher than those of conventional PD without increasing morbidity [67-69]. Recurrence rate after MpE was significantly lower than that after conventional PD (Table 7) [67,70]. However, MpE did not result in improved survival [68].

Because of low-level evidence derived from a small number of retrospective studies, MpE should not be generally recommended, although MpE is a feasible procedure. It might be

Table 7. Summary of retrospective cohort studies of mesopancreas excision (MpE)

Author	Comparison group	Number	Morbidity (%)	*p*-value	R0 (%)	*p*-value	Recurrence (%)	*p*-value	1YSR (%)	*p*-value
Kawabata et al. [67]	C-PD	25	56	0.546	60	0.019	64	0.036	48	N/A
	MpE	14	50		93		14		76	
Aimoto et al. [70]	C-PD	19	32	NS	68	NS	37	< 0.01	70	NS
	MpE	19	47		74		0		60	
Sugiyama et al. [69]	C-PD	45	39	0.078	78	0.099	NA		N/A	
	MpE	58	28		90					
Xu et al. [68]	C-PD	43	51	0.250	77	0.041	55	0.054	20 mo[a)]	0.176
	MpE	58	40		91		32		23 mo	

1YSR, 1-year survival rate; C-PD, conventional pancreaticoduodenectomy; NA, not available; NS, not significant.
[a)]Median overall survival.

performed in limited cases to achieve R0 resection. Further studies with long-term survival data are needed to confirm the benefits of MpE.

Pylorus preserving pancreaticoduodenectomy (PPPD) vs. pancreaticoduodenectomy (PD)

KQ 6: Is PPPD preferred to PD in RPHC?

Recommendation 6: PPPD is preferred to PD in RPHC
(Strength of recommendation: Conditional;
Level of evidence: High)

Comments: To date, the debate continues as to whether PPPD or PD is better for periampullary and pancreatic carcinoma. Three RCTs and three meta-analyses have compared PPPD and PD in terms of complications and nutritional status [71-76]. There were no significant differences in postoperative morbidity including pancreatic fistula, postoperative bleeding, or hospital mortality between PPPD and PD groups, although there were controversial results on delayed gastric emptying. For long-term complications including weight loss, dumping syndrome, diarrhea and long-term nutritional status, there were no significant differences between PPPD and PD groups [73,77]. Therefore, both surgical procedures are acceptable for the treatment of pancreatic carcinoma. Surgeons can choose either operative method based on their preferences. If there are no differences in oncological or nutritional aspects, PPPD should be preferred in terms of organ preservation.

Intraoperative frozen biopsy for pancreatic resection margin

KQ 7: Is additional pancreas resection necessary in cases of positive pancreatic resection margin in intraoperative frozen biopsy?

Recommendation 7: Additional pancreas resection could be considered if pancreatic resection margin is positive in intraoperative frozen biopsy
(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments: Several reports have compared the survival of patients between those who have undergone an additional resection and finally have negative pancreatic resection margin and those who have not undergone additional resection in spite of positive resection margin or who have positive resection margin after additional pancreatic resection [78-85]. Except for two studies that failed to perform survival analysis due to the small number of included patients [79,82], the remaining retrospective studies showed controversial results in survival outcome [78,80,81,83]. Meta-analysis and systematic review did not demonstrate survival benefit after additional pancreatic resection in giving a negative margin [84,85].

The aggressive biology of pancreatic cancer might be associated with the unexpected result that revision of an R1 pancreatic resection margin based on intraoperative frozen biopsy could not improve overall survival. However, considering that obtaining negative resection margin is the principle of surgery in oncology, surgeons should try to perform additional pancreatic resection to achieve a negative resection margin.

Radical antegrade modular pancreatosplenectomy (RAMPS)

KQ 8: Is RAMPS beneficial in pancreatic body or tail cancer?

Recommendation 8: RAMS could be considered in pancreatic body or tail cancer
(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments: In 2003, Strasberg et al. [86] introduced a novel approach to resect a pancreatic adenocarcinoma in the body and tail (RAMPS) to increase the rate of R0 resection and lymph node yield. In a meta-analysis (conventional DP group, n = 150; RAMPS group, n = 135), RAMPS showed a higher R0 resection rate (RR = 2.37, 95% CI [1.19–4.72]; p = 0.01) and more lymph nodes harvested (RR = 1.20, 95% CI [1.02–1.41]; p = 0.02) than conventional DP. The one-year survival rate of the RAMPS group was significantly better than that of the DP group (79.2% [99/125] vs. 64.3% [81/126]; p = 0.02), while the long-term survival benefit was not demonstrated [87]. However, among retrospective studies, Sham et al. [88] included the largest number of patients and showed controversial results that the R0 resection rate and the number of retrieved lymph nodes were higher in the conventional DP group than in the RAMPS group. Most retrospective studies showed a higher R0 resection rate and a higher number of retrieved lymph nodes in the RAMPS group than in the conventional DP group, although the benefit of survival was not demonstrated (Table 8) [88-93].

RAMPS is a safe and effective procedure for pancreatic body or tail cancer. However, it does not lead to a better survival than conventional DP. Therefore, the technical approach to pancreatosplenectomy could be selected based on the surgeon's experience and comfort. RAMPS could be considered for curative resection of selected patients.

Gastrojejunostomy as bypass surgery

KQ 9: Is prophylactic bypass gastrojejunostomy necessary in cases of unresectable pancreatic cancer without gastric outlet obstruction?

Recommendation 9: Bypass gastrojejunostomy is not recommended in patients with unresectable pancreatic cancer without gastric outlet obstruction
(Strength of recommendation: Not recommend;
Level of evidence: Low)

Comments: A patient with unresectable pancreatic cancer found during laparotomy traditionally undergoes a prophylactic bypass gastrojejunostomy. Two old RCTs and meta-analysis

Table 8. Summary of retrospective studies comparing radical antegrade modular pancreatosplenectomy (RAMPS) and conventional distal pancreatectomy (C-DP)

Author	Number	Factors	RAMPS	C-DP	*p*-value
Abe et al. [89]	53/40	R0 resection (%)	90.5	67.5	< 0.005
		LN counts	28.4 ± 11.6	20.7 ± 10.1	0.001
Grossman et al. [90]	78/0	R0 resection (%)	66	-	
		LN counts	20.0 ± 12.2		
Kim et al. [91]	26/17	R0 resection (%)	96	64	0.15
		LN counts	21.5 ± 8.3	13.7 ± 7.4	0.03
Kawabata et al. [92]	66/0	R0 resection (%)	89	-	
		LN counts	27 ± 15		
Sham et al. [88]	253/193	R0 resection (%)	89	94	0.01
		LN counts	12	18	< 0.001
Kim et al. [93]	53/53	R0 resection (%)	59	77	0.37
		LN counts	15.81 ± 10.25	13.36 ± 9.8	0.21

Values are presented as mean ± standard deviation.
LN, lymph node.

showed that prophylactic gastric bypass surgery in cases of unresectable pancreatic cancer was effective in preventing gastric outlet obstruction without serious complications [94-96]. However, with recent advances in endoscopic techniques, surgical bypass has become questionable. In a recently published meta-analysis, endoscopic stent was found to have benefits of a quicker resumption of oral intake and a reduced inpatient hospital stay. However, this was balanced by an increase in the recurrence of symptoms and the need for further intervention [97]. Williamsson et al. [98] have introduced a wait-and-see strategy considering the higher morbidity and longer postoperative stay after surgical bypass. Patients without gastric outlet obstruction could not undergo prophylactic bypass.

For patients with pancreatic cancer without gastric outlet obstruction, the effect of prophylactic bypass is controversial. However, for patients with gastric outlet obstruction, endoscopic stent insertion could be performed as it is associated with lower morbidity and shorter hospital stay than surgical bypass.

Pancreatectomy in case of pathologically proven para-aortic lymph node metastasis

KQ 10: Is pancreatectomy beneficial in cases of pancreatic cancer with pathologically proven para-aortic lymph node metastasis in intraoperative frozen biopsy?

Recommendation 10: Recommendation to perform pancreatectomy in cases of pancreatic cancer with pathologically proven para-aortic lymph node metastasis in intraoperative frozen biopsy is withheld
(Strength of recommendation: Inconclusive;
Level of evidence: Very low)

Comments: In general, para-aortic lymph node metastasis is considered a distant metastasis and contraindication for pancreatic resection. However, some pancreatic cancer patients with para-aortic lymph node metastasis have been reported to have longer survival than expected after pancreatectomy. However, no study has compared survival outcomes between pancreatectomy and non-pancreatectomy groups for patients with intraoperatively pathologically proven positive para-aortic lymph nodes and curatively resectable main pancreatic tumor. Previously published studies showed that the median survival of patient with intraoperatively pathologically proven para-aortic lymph node was 5–9 months, significantly worse than that of patients with negative para-aortic lymph node [99,100]. However, recently published studies showed improved median survival of patients with pathologically proven para-aortic lymph nodes in frozen biopsy. Multivariate analysis demonstrated that adjuvant chemotherapy, but not para-aortic lymph node metastasis, was a significant prognostic factor [101-103]. In meta-analyses, although para-aortic lymph node metastasis is associated with decreased survival in pancreatic cancer, based on the finding that those who underwent pancre-

atectomy had long-term survival, further study is needed to determine characteristics of long-term survivors and indication for pancreatectomy [104,105]. Asaoka et al. [106] recommend pancreatectomy for patients with a CA19-9 level less than 360 U/mL. Currently, when the para-aortic lymph node is pathologically confirmed as metastasis intraoperatively, pancreatectomy is deemed controversial. Although several long-term survivors who underwent pancreatectomy followed by adjuvant chemotherapy, further studies comparing oncologic outcomes between pancreatectomy and non-pancreatectomy groups with positive para-aortic lymph nodes are needed.

Hepatic oligometastasis

KQ 11: Is hepatic resection beneficial in cases of pancreatic cancer with hepatic oligometastasis?

Recommendation 11: Recommendation to perform hepatic resection in cases of pancreatic cancer with hepatic oligometastasis is withheld

(Strength of recommendation: Inconclusive;
Level of evidence: Very low)

Comments: The prognosis of patients with liver metastasis from pancreatic cancer is generally regarded as dismal and hepatic resection is not recommended. However, in highly selected patients, hepatectomy showed a survival benefit. Hackert et al. [107] showed that the median survival was 12.3 months and the 5-year survival rate was 8.1% after hepatectomy for oligometastasis. On the other hand, Zanini et al. [108] showed that the median survival of patients who underwent hepatectomy for oligohepatic metastasis was only 9.1 months. Dünschede et al. [109] reported that for patients with metachronous hepatic oligometastasis, hepatectomy showed significantly better median survival than chemotherapy (31 months vs. 11 months). A meta-analysis found that for patients with synchronous hepatic oligometastasis, hepatectomy showed significantly better 1- or 3-year survival than non-resection [110].

Considering the increased number of reports showing improved survival after hepatectomy for hepatic oligometastasis, it is worthwhile to perform curative intended hepatectomy. However, further RCTs are needed to investigate indications for hepatectomy and prognostic factors associated with hepatectomy.

Induction chemotherapy and conversion surgery for locally advanced pancreas cancer

KQ 12: Is conversion surgery beneficial in cases of LAPC?

Recommendation 12: Conversion surgery after induction chemotherapy could be considered in cases of LAPC

(Strength of recommendation: Conditional;
Level of evidence: Low)

Comments: LAPC has been generally considered to be an unresectable disease. Historically, it was considered a continuum of metastatic disease due to rapid progression of occult metastasis. However, an increasing number of patients with LAPC who respond favorably to induction chemotherapy undergo surgical resection. Most published studies including two RCTs showed improvement of survival in conversion surgery after induction chemotherapy for LAPC [111-116]. Meta-analyses also showed significantly better survival in the conversion surgery group than in the non-surgery group [117,118]. However, evaluation of resectability of pancreatic cancer after induction chemotherapy is challenging. In addition, several indications do not have consensus, such as patients with complete or partial response according to RECIST classification (ver 1.1) after neoadjuvant chemotherapy, after multidisciplinary discussion, after diagnostic laparoscopy, and so on.

Conversion surgery after induction chemotherapy for LAPC could be considered in highly selected patients and should be considered in individual cases. Further studies are needed to investigate indications for resection after induction chemotherapy and effective chemotherapy protocols.

Artery first approach

KQ 13: Is artery first approach in pancreaticoduodenectomy (AFA-PD) beneficial in cases of PHC?

Recommendation 13: Recommendation to perform AFA-PD in cases of PHC is withheld

(Strength of recommendation: Inconclusive;
Level of evidence: Very low)

Comments: SMA, the most common site of a positive margin following PD, is often the last and the most challenging one to dissect, typically after division of the neck of the pancreas. AFA-PD aims to determine the resectability before the point of no return (transection of the pancreatic neck or bile duct division) to reduce intraoperative blood loss by early control of blood inflow into the pancreatic head and to increase the R0 resection rate and complete dissection of the connected tissues around the SMA. Despite the above theoretical benefits of this procedure, evidence for its clinical and oncological benefits is sparse. Most published reports of AFA-PD showed less bleeding [70,119,120] but no difference in operation time [70,120-122] or postoperative complications [70,119-122]. However, there was no significant difference in R0 resection rate and the 5-year

Table 9. Summary of retrospective studies comparing artery first approach in pancreaticoduodenectomy (AFA-PD) and conventional pancreaticoduodenectomy (C-PD)

Author	Comparison group	Number	Op time (min)	*p*-value	Blood loss (mL)	*p*-value	R0 rate (%)	*p*-value	LN harvest (n)	*p*-value	Morbidity (%)	*p*-value	Survival (%)	*p*-value
Kurosaki et al. [121]	C-PD	35	526	0.651	1,352	0.814	71.4	1.00	N/A		42.9	0.352	17.1[a]	0.016
	AFA-PD	40	516		1,307		72.5				30.0		52.8	
Aimoto et al. [70]	C-PD	19	481	NS	1,568	< 0.05	68	NS	3.4	< 0.01	10	NS	40[b]	NS
	AFA-PD	19	490		490		74		7.9		20		20	
Hirono et al. [119]	C-PD[c]	30	371	0.007	502	0.023	86.7	0.045	23.5	0.919	10	0.386	N/A	0.021
	AFA-PD	28	417		313		100		23		17.9			
	C-PD[d]	28	452	0.210	920	0.003	85.7	0.565	26	0.668	17.9	0.634	N/A	0.260
	AFA-PD	30	459		508		80.0		26.5		13.3			
Pędziwiatr et al. [122]	C-PD	19	425	0.13	392	0.33	63.2	0.84	139.	0.03	63.2	0.84	N/A	N/A
	AFA-PD	12	467		408		66.7		19.3		66.7			
Wang et al. [120]	C-PD	39	384	0.014	756	0.043	82.1	0.534	N/A		46.2	0.603	N/A	N/A
	AFA-PD	78	313		534		83.3				41.0			

OP, operation; LN, lymph node; N/A, not available; NS, not significant.
[a]Three-year survival rate; [b]2-year survival rate; [c]resectable pancreas cancer; [d]borderline resectable cancer.

survival rate could not be evaluated due to a short follow-up period (Table 9) [70,119-122]. Recently, Sabater et al. [123] have performed a RCT of patients with periampullary cancers and found no difference in R0 resection rate. Therefore, although AFA-PD is a feasible procedure, the benefit of this procedure such as improvement of resectability and survival has not been proven.

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