Asian Journal of Surgery 46 (2023) 166–173

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Intraoperative pancreatoscopy in pancreaticoduodenectomy for intraductal papillary mucinous neoplasms of the pancreas: Application to the laparoscopic approach

Hye yeon Yang [a, b], Incheon Kang [c, #], Ho Kyoung Hwang [a, b], Woo Jung Lee [a, b], Chang Moo Kang [a, b, *]

[a] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, South Korea
[b] Pancreatobiliary Cancer Center, Yonsei Cancer Center, Severance Hospital, Seoul, South Korea
[c] Division of HBP and Transplantation Surgery, Department of Surgery, CHA Bundang Medical Center, CHA University, South Korea

ARTICLE INFO

Article history:
Received 30 August 2021
Received in revised form
30 December 2021
Accepted 3 March 2022
Available online 21 March 2022

Keywords:
Frozen sections
Pancreas
Pancreatic duct
Pancreatic intraductal neoplasms
Pancreaticoduodenectomy

SUMMARY

Background: /Purpose: Owing to the characteristics of IPMNs, which have variable skipped lesions along the main pancreatic duct (MPD), determining the surgical margins is very difficult. This study aimed to investigate the efficacy and potential oncologic impact of intraoperative pancreatoscopy (IOP) compared to frozen section biopsy (FSB) in pancreaticoduodenectomy (PD) for pancreatic head IPMNs.
Methods: Data of patients who underwent PD for IPMNs of the pancreas between October 2007 and May 2020 were retrospectively reviewed. IOP was performed in selected patients with IPMNs with inconclusive MPD involvement based on preoperative evaluations. Patients were divided into two groups, IOP group, FSB group. Clinicopathologic features and oncologic outcomes were compared between two groups.
Results: 60 patients underwent PD (laparoscopic or robotic, 42; open, 18) for pancreatic head IPMNs. IOP was safely performed in 28 patients, including minimally invasive approach used in 21 patients (35%). IOP group had a significantly larger MPD size (9.15 ± 4.79 mm vs 6.43 ± 4.11 mm, $p = 0.021$). Based on IOP, the initial surgical plan could be changed in 5 patients (17.8%) for complete resection. Recurrence occurred in 2 patients in FSB group and 3 patients in IOP group during the follow-up period (33.2 months, [range, 3.5–131.4 months]). Overall disease-free survival rate did not significantly differ between two groups ($p = 0.529$).
Conclusions: IOP can be safely performed in patients with pancreatic head IPMNs with MPD dilatation, even in the laparoscopic approach. Further studies evaluating the long-term oncologic effect of IOP for the management of IPMNs are required.

1. Introduction

The widespread use of computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) has led to the increased detection of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, often as an incidental finding.[1,2] IPMNs are characterized by intraductal proliferation of mucin-producing epithelial cells,[3] resulting in dilatation of the main pancreatic duct (MPD) and/or its branches, and can be malignant, transforming to adenocarcinomas.[4]

International consensus guidelines for the management of IPMNs of the pancreas, which were recently revised in 2017, have steadily evolved. According to the recent international consensus Fukuoka guidelines for the management of IPMNs of the pancreas, surgery should be considered when IPMNs is associated with high risk of malignancy.[5] The aim of surgical resection is to achieve complete tumor removal without leaving “skipped” lesions. However, owing to the characteristics of IPMNs, which have variable

* Corresponding author. Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, South Korea.
E-mail address: CMKANG@yuhs.ac (C.M. Kang).
# Contributed equally to this work as first author.

https://doi.org/10.1016/j.asjsur.2022.03.003

skipped lesions along the pancreatic duct, ranged 6–21%,[6–8] determination of the appropriate surgical margins is sometimes very difficult.

Despite advancement in imaging techniques, preoperative imaging modalities (CT, endoscopic retrograde cholangiopancreatography, EUS, magnetic resonance cholangiopancreatography [MRCP]) have many limitations with respect to the identification of skipped lesions in the pancreatic duct system.[8,9] Therefore, in such cases with IPMNs involving the MPD, recent researches recommended that preoperative per-oral pancreatoscopy (POPS) could provide the extent of the tumor before surgical resection as direct visualization of the MPD.[10–12] In addition, intraductal ultrasonography, intraoperative cytology, and frozen section biopsy (FSB) have been used to obtain additional information on adequate surgical margin in selected patients.[13–15]

Among these, intraoperative FSB has been used as standard assessment to adequate margin to date.[16] However, FSB should be carefully analyzed, because the absence of borderline lesion or tumor cells in the frozen section analysis does not always warrant absence of an adjacent tumor.[17] Although a clear margin could be achieved by FSB, a real negative resection margin could not be assured for discontinuous lesions,[6] leading to a potential for recurrence.[18–20]

Intraoperative pancreatoscopy (IOP) was first introduced to overcome this difficulty in 1998.[21] As a direct visualization of the MPD, IOP can be used to detect skipped lesion of the remnant pancreas. Recent studies suggest the potential application of IOP to define the appropriate margin for the management of IPMNs of the pancreas.[22–24] Yelamali et al[22] showed that IOP with narrow band imaging is a good diagnostic tool that could help in intraoperative decision-making regarding resection margin in IPMNs. Pucci et al[23] applied IOP to 18 patients with main-duct IPMNs and concluded that the selective use of intraoperative fiberoptic endoscopy to evaluate the pancreatic duct appeared to help surgeons perform appropriate resection and optimal treatment. Moreover, Navez et al[24] suggested that IOP for the MPD combined with intraductal biopsies plays a significant role in the surgical management of patients with IPMNs.

However, there have been no studies evaluating the long-term oncologic outcome of IOP for IPMNs. Therefore, in this study, we investigated efficacy and potential oncologic impact of IOP compared to FSB in pancreaticoduodenectomy (PD) for pancreatic head IPMNs. Additionally, we present our experience with using IOP for IPMNs of the pancreas, especially laparoscopic approach.

2. Materials and methods

2.1. Patients and data collection

The study protocol was approved by the institutional review board (IRB) of Yonsei University College of Medicine (IRB number 2018-0862-001). Data of all patients who underwent PD for IPMNs of the pancreas head performed by a single surgeon (C.M. Kang) between October 2007 and May 2020 were acquired from electronic medical record systems and retrospectively reviewed. All patients underwent CT, MRCP, and EUS to preoperatively evaluate the characteristics of IPMNs and IPMNs characteristics were classified into three types, main duct type IPMNs (MD-IPMN), branch duct type IPMNs (BD-IPMN), and mixed type IPMNs (Mix-IPMN) on the results of CT, MRCP, and EUS. Based on preoperative imaging studies, the following criteria were indicated for IOP to define the extent of surgical resection of the pancreas; 1) MD-IPMN or 2) suspicious Mix-IPMN or 3) inconclusive MPD involvement. This group was defined as IOP group and confirmed the negative resection margin by FSB again. All those who did not perform IOP were applied intraoperative FSB to achieve adequate surgical margin as a standard method. We defined this group as FSB group. Clinicopathologic features and oncologic outcomes were compared between two groups. This study was approved by the institutional review board of Severance Hospital (IRB No.04-2018-0338), which waived the requirement for informed consent due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

2.2. Postoperative follow-up

All patients were regularly followed up to assess their serum tumor marker levels (e.g. CA 19-9 and CEA) and perform imaging studies (e.g. CT and/or MRI) beginning 3–6 months after discharge. Recurrence was defined as suspicious imaging findings or a pathologically proven tumor from a biopsy/surgery. Disease-free survival (DFS) was defined as the duration from the date of initial resection to the date of tumor recurrence.

2.3. Laparoscopic technique of intraoperative pancreatoscopy

IOP technique performed in open procedure were described in previous studies.[23,24] We also conducted IOP in laparoscopic approach as well as open procedure. Therefore, we present our laparoscopic IOP technique in this section. The laparoscopic PD technique used in our institution had been previously published.[25,26] The patient was placed in the supine position on the operating table and underwent general endotracheal anesthesia. As our usual method, three 5-mm trocars (above) and three 12-mm trocars (below) were used in laparoscopic PD procedure (Fig. 1A). Laparoscopic scope was inserted to right sided 12-mm trocar (Fig. 1A) and it can allow to see the whole intra-abdominal view (Fig. 1B). According to preoperative imaging diagnosis, initial resection margin of pancreas head IPMNs was decided. At this point, to minimize and avoid the risk of peritoneal dissemination from pancreatic juice leakage, the pancreas was resected using the Endo GIA staplers. And then, additional segment (about 1 cm margin) of the remnant pancreas was divided by ultrasonic shears or scissors to exposure final cut surface of the remnant pancreas with MPD. The 3 or 5 mm ultrathin flexible pancreatoscope with Olympus camera guided by grasper was inserted to MPD for exploring the remnant pancreas (Fig. 1C). In next, we could evaluate the entire remnant pancreatic ductal condition through the continuous normal saline irrigation to obtain a clear image and keep trying to find skipped lesion of pancreatic duct, such as papillary projections, mural nodule, and other atypical lesions (Figs. 1c–2). When the proper margin (red dotted line) was determined, turn off the intraabdominal laparoscopic light, we made a mark on the outside of pancreatic duct that looks normal with a monopolar hook by using transilluminated light of pancreatoscope (Fig. 1c–) Finally, pancreas was re-transected with newly determined margin (Fig. 1D).

2.4. Statistical analysis

All statistical analyses were performed using SPSS statistics software version 25 (IBM corporation, Armonk, NY). Continuous variables were summarized and reported as means with standard deviations or medians and interquartile ranges. Categorical variables were summarized and reported as frequencies and percentages. Statistical analyses were performed with a t test or Chi-square test, as appropriate. Survival was assessed with Kaplan–Meier analyses. Survival outcomes were compared using log-rank tests. Statistical significance was set at a p-value <0.05.

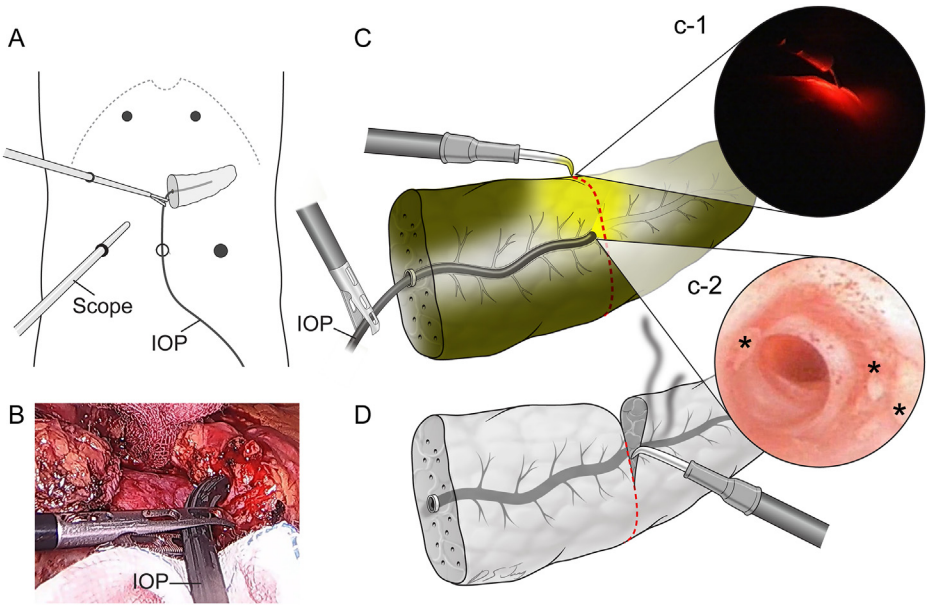

Fig. 1. Illustration of laparoscopic IOP
A. Outside view of laparoscopic pancreaticoduodenectomy with IOP.
B. Real operation view. 3 mm or 5 mm sized IOP was performed to evaluate the MPD in remnant pancreas.
C. Extent of pancreatic resection can be modified under the guidance of IOP findings.
c-1 Marking with a monopolar hook at the site of normal-looking pancreatic duct using transilluminated light of pancreatoscope.
c-2 Real pancreatoscope view. Note some small nodules (*) in the remnant main pancreatic duct, which was not preoperatively detected.
D. Re-transection of pancreas is performed by newly determined resection line (red dotted line)
IOP, intraoperative pancreatoscopy; MPD, main pancreatic duct.

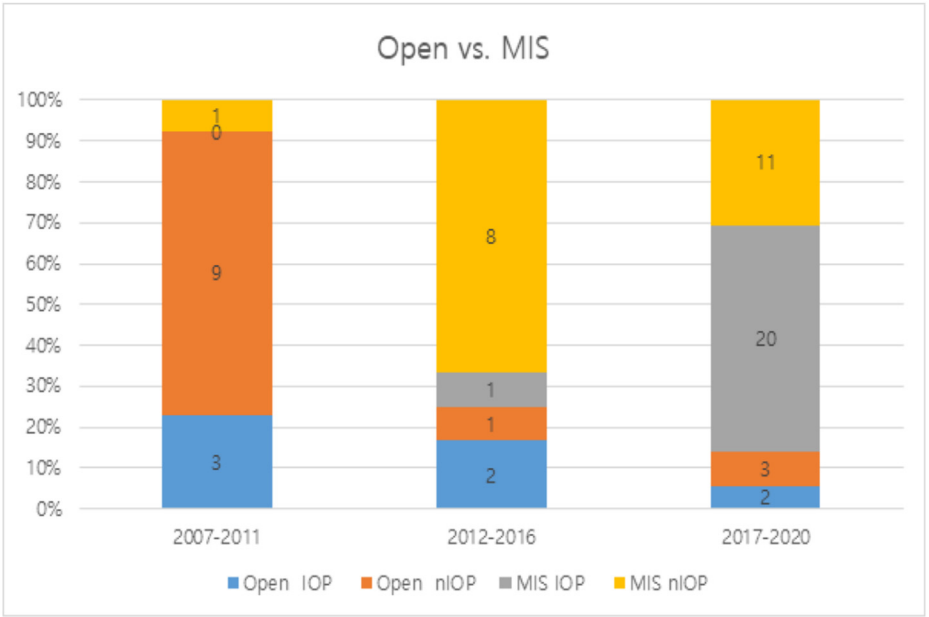

Fig. 2. Chronological changes in surgical approach to pancreatic head IPMNs and Application of IOP according to surgical approach in time period.
IOP, intraoperative pancreatoscopy; MIS, minimally invasive surgery; IPMNs, intraductal papillary mucinous neoplasm.

3. Results

3.1. Patient demographics

A total of 60 patients (mean age, 64.4 ± 7.7 years [range, 43–82 years]; 42 males [70%], 18 females [30%]) underwent PD for pancreatic head IPMNs between October 2007 and May 2020. All patients were histologically confirmed as having IPMNs. According to IPMNs type, there were 13 MD-IPMN (21.6%), 30 BD-IPMN (50%), and 17 Mix-IPMN (28.4%) preoperatively (Table 1).

Of patients, 18 (30%) underwent open pylorus-preserving pancreaticoduodenectomy (OPD), whereas 42 (70%) underwent laparoscopic PD. The use of laparoscopic approach steadily increased from 2007 to 2020 (Fig. 2), with a significant increase in the number

Table 1
Baseline characteristics of resected pancreatic head IPMNs.

Baseline characteristic	Total (N = 60)
Age (range)	64.4 ± 7.71 [range, 43–82]
Gender	
Male	42 (70%)
Female	18 (30%)
Surgical approach	
Open	18 (30%)
MIS (Laparoscopic or Robotic)	42 (70%)
IPMN type	
	14 (23.3%)
BD-IPMN	30 (50%)
Mix-IPMN	16 (26.4%)
IOP	
No	32 (53.3%)
Yes	28 (46.4%)
Follow up period, months (range)	33.2 [range, 3.5–131.4]

IPMNs, intraductal papillary mucinous neoplasm; MD-IPMN, main duct type IPMNs; BD-IPMN, branch duct type IPMNs; Mix-IPMN, mixed type IPMNs; IOP, intraoperative pancreatoscopy

of cases of laparoscopic approach within this period ($p < 0.0001$). Similarly, the application of IOP in laparoscopic surgery increased within the same period ($p = 0.021$).

3.2. Comparative analysis between the IOP group and FSB group

IOP for the assessment of the MPD was intraoperatively performed in 28 (46.6%) out of 60 patients (21, MISPD; 7, OPD). It took approximately 15 min to perform the IOP procedure. No IOP-related complications were noted. Comparison of perioperative clinicopathologic features between the IOP group and FSB group is summarized in Table 2. Preoperatively, there were no significant differences in age/gender, previous surgical history, surgical approach (laparoscopic, robotic vs open), American Society of Anesthesiologists score, and carcinoembryonic antigen. levels between two groups ($p > 0.05$). Only carbohydrate antigen 19-9 showed difference between two groups ($p = 0.039$). According to the pathology report, all patients achieved margin free operation. Furthermore, malignancy rate showed no difference between two groups. (21.4% in IOP group, 31.2% in FSB group, $P > 0.438$).

Moreover, the MPD was significantly larger in the IOP group (9.15 ± 4.79 mm vs 6.43 ± 4.11 mm, $p = 0.021$). Intraoperative parameters (mean operative time, blood loss, transfusion) and postoperative pancreatic fistula (by 2016 International Study Group definition[27]) and length of hospital day were not significantly different between two groups ($p > 0.05$). All patients underwent R0 resection. No mortality during the perioperative period was reported in both groups. The median follow-up duration was 21.82 months in the IOP group and 43.2 months in the FSB group ($p = 0.023$).

3.3. Oncologic outcomes of IOP in PD for pancreatic head IPMNs

The results for 28 patients who underwent PD with IOP are summarized in Table 3. We identified 5 patients (17.8%) with skipped lesions that were potentially missed; these patients required additional resection based on IOP findings. After a median follow-up of 33.3 months period (range, 3.53–131.4 months), five patients (8.3%, 3 patients in the IOP group and 2 patients in the FSB group, respectively) had tumor recurrence and one (1.6%) died. The recurrence pattern in each patient was summarized in Table 4. Tumor recurrence was noted in the patient at approximately 100.3 months, 15.1 months, 22.4 months, 3.9 months, and 13.4 months after pancreatectomy, respectively. The 5-year DFS rate was 82.7% in the IOP group ($n = 26$ of 28) and 91.5% in the FSB group ($n = 30$ of 32). There was no significant difference in disease free survival rate between IOP group and FSB group ($p = 0.225$, Fig. 3).

4. Discussion

According to the recent international consensus Fukuoka guidelines for the management of IPMNs of the pancreas, surgery should be considered when IPMNs is associated with any of "high-risk stigmata" or "worrisome features" along with definite mural nodule ≥5 mm, MPD involvement, and suspicious or positive in cytologic findings.[5] However, in clinical circumstances, surgeons

Table 2
Perioperative clinicopathologic features between the IOP group and FSB group.

	IOP group (28)	FSB group (32)	p-value
Age (years)	66.36 ± 6.30	62.59 ± 8.49	0.066
Gender (Male/Female)	18/10	24/8	0.366
Previous operation (No/Yes)	12/16	20/12	0.128
Surgical Approach (Open/MIS)	7/21	12/20	0.429
ASA (1/2/3/4)	4/13/11/0	4/16/12/0	0.957
CEA (U/mL)	17.23 ± 78.35	3.14 ± 2.64	0.313
CA 19-9 (U/mL)	17.22 ± 21.04	44.48 ± 65.51	**0.039**
MD-IPMN/BD-IPMN/Mix-IPMN	9/12/7	5/8/19	0.311
MPD size (mm)	9.15 ± 4.79	6.43 ± 4.11	**0.021**
Cyst size (mm)	34.81 ± 15.96	39.34 ± 16.37	0.289
Mural nodule (No/Yes)	16/12	19/13	0.861
Pathology (benign/non-invasive/invasive)	13/9/6	16/6/10	0.438
Margin status (R0/R1/R2)	28/0/0	32/0/0	NA
Remnant pancreas reconstruction (PJ/PG)	4/24	4/28	0.839
Operation time (min)	423.29 ± 71.01	423.29 ± 71.01	0.147
EBL (mL)	213 ± 140	343 ± 326	0.058
Intraoperative transfusion (No/Yes)	28/0	30/2	0.178
POPF (No,BL/B/C)	13/13/2	16/14/2	0.960
LOH (days)	17.11 ± 6.63	17.03 ± 5.56	0.962
Recurrence (No/Yes)	26/2	30/2	0.890
Follow up period (months)	21.82 ± 26.56	43.20 ± 41.39	**0.023**

IOP, intraoperative pancreatoscopy; FSB, frozen section biopsy; PPPD, pylorus-preserving pancreaticoduodenectomy; MIS, minimally invasive surgery; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; MD-IPMN, main duct type IPMNs; BD-IPMN, branch duct type IPMNs; Mix-IPMN, mixed type IPMNs; MPD, main pancreatic duct; PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy; EBL, estimated blood loss; POPF, postoperative pancreatic fistula; BL, biochemical leak; LOH, length of hospitalization.

Table 3
Summary of total cases of IOP.

No.	Age /Gender	IPMNs Type	IOP finding (skipped lesion)	Pathology	Additional resection	Recur
1	72/F	BD-IPMN	No	Benign	No	No
2	65/M	MD-IPMN	No	Non-invasive	No	Yes
3	74/M	Mix-IPMN	No	Non-invasive	No	No
4	75/M	Mix-IPMN	No	Non-invasive	No	No
5	71/M	Mix-IPMN	No	Benign	No	No
6	55/M	BD-IPMN	No	Benign	No	No
7	76/F	Mix-IPMN	No	Invasive, N0	No	No
8	72/M	BD-IPMN	No	Invasive, N0	No	No
9	65/F	MD-IPMN	Yes	Invasive, N0	Yes	No
10	66/M	Mix-IPMN	No	Benign	No	Yes
11	63/M	MD-IPMN	No	Benign	No	No
12	60/M	Mix-IPMN	Yes	Benign	Yes	No
13	63/M	Mix-IPMN	No	Benign	No	No
14	67/M	MD-IPMN	No	Benign	No	No
15	62/M	Mix-IPMN	Yes	Non-invasive	Yes	No
16	63/F	BD-IPMN	No	Invasive, N0	No	No
17	70/F	MD-IPMN	Yes	Non-invasive	Yes	No
18	82/F	MD-IPMN	No	Invasive, N1	No	Yes
19	69/F	BD-IPMN	No	Non-invasive	No	No
20	63/M	BD-IPMN	No	Non-invasive	No	No
21	59/M	BD-IPMN	No	Benign	No	No
22	63/F	BD-IPMN	No	Benign	No	No
23	65/M	BD-IPMN	No	Invasive, N0	No	No
24	64/F	BD-IPMN	No	Benign	No	No
25	65/M	BD-IPMN	No	Benign	No	No
26	53/M	MD-IPMN	No	Non-invasive	No	No
27	67/M	MD-IPMN	Yes	Non-invasive	Yes	No
28	69/F	BD-IPMN	No	Benign	No	No

IOP, intraoperative pancreatoscopy, IPMNs, intraductal papillary mucinous neoplasms; MD-IPMN, main duct type IPMNs; BD-IPMN, branch duct type IPMNs; Mix-IPMN, mixed type IPMNs.

Table 4
Recurrence pattern of resected pancreatic head IPMNs.

	Age /Gender	IOP finding	Margin status	Pathology	Recurrence site	Recurrence period
1	65/Male	Normal	R0	Moderate grade dysplasia	Multiple liver & lung metastasis	100.3 months, alive
2	75/Male	NA	R0	Invasive, 4.5 cm LN, 2/17	Multiple liver metastasis, peritoneal seeding	15.1 months, death
3	66/Male	Normal	R0	Low grade dysplasia	Mucinous seeding lesions in the perihepatic space suggesting recurrence as pseudomyxoma peritonei	22.4 months, alive
4	82/ Female	Normal	R0	Invasive, 3.6 cm, LN, 3/ 13	Liver, peribiliary, pancreas anastomosis site	3.9months, alive
5	62/ Female	NA	R0	High grade	Remnant pancreas	13.4months, alive

IPMNs, intraductal papillary mucinous neoplasm; IOP, intraoperative pancreatoscopy; NA, not applicable; LN, lymph node.

need to define not only the surgical indications but also the appropriate surgical extent to manage IPMNs of the pancreas. From that point of view, IPMNs with MPD dilatation may be one of the most challenging problems.

There are two possible scenarios for IPMNs with MPD dilatation: (1) actual involvement of IPMNs, which can be suspected based on preoperative imaging findings, such as MPD wall thickening and presence of mural nodules, and (2) secondary dilatation due to mucin stagnation in the pancreatic duct system. Distinguishing these two different clinical situations is thought to be very important, because the extent of surgical resection should be determined.

Taking into consideration that IPMNs are low-grade malignant tumors and that relative long-term survival is highly expected after surgery,[28] the extent of surgical resection can be directly associated with pancreatic endocrine and exocrine function and quality of life.[29] In our series, almost all cases of MPD dilatation were fortunately determined to be secondary changes due to mucin stagnation, and unnecessary total pancreatectomy could be avoided. However, 5 patients (17.8%) had IPMNs associated with skipped lesions based on IOP findings, altering the planned surgical extent for the removal of all potential lesions. This observation appears to be similar in other previous studies. Pucci et al[23] reported that the surgical extent needed to be changed in 22% of patients based on IOP findings. Navez et al[24] reported that IOP performed in 21 patients with IPMNs associated with MPD dilatation revealed 8 occult IPMN lesions, and the initially planned surgical resection was modified in 23.5% of patients based on IOP findings.

Because IPMNs often have synchronous or metachronous multicentric lesions,[7,30] several authors advocate total pancreatectomy as a treatment option for IPMNs with diffuse MPD dilatation to minimize the risk of recurrence of remnant pancreatic lesion.[31,32] This suggests the difficulty in achieving an appropriate resection margin for the treatment of IPMNs. However, the performance of unnecessary total pancreatectomy would be avoided, preventing

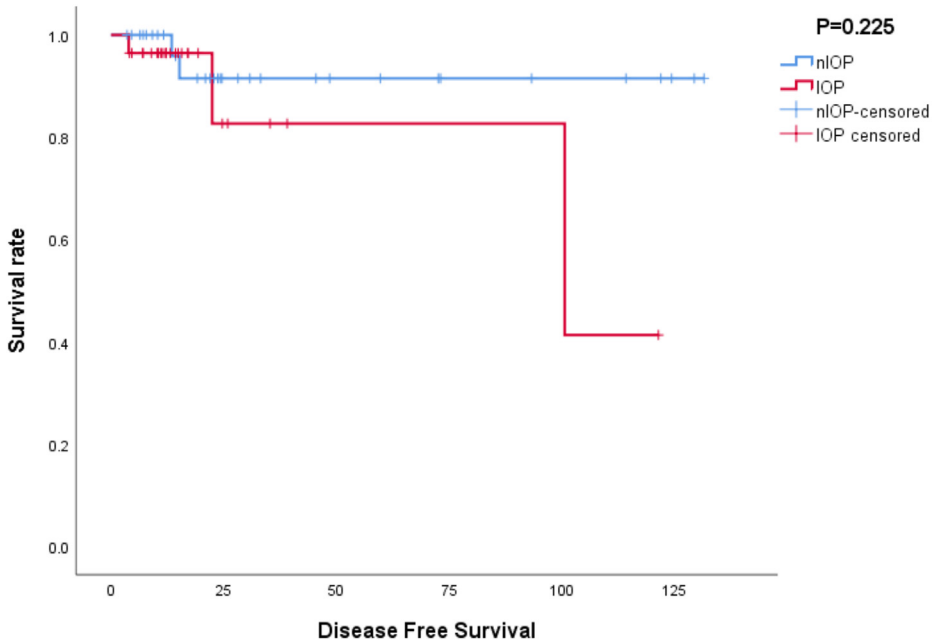

Fig. 3. Oncologic effect of IOP on the recurrence of resected pancreatic head IPMNs.
IOP, intraoperative pancreatoscopy; IPMNs, intraductal papillary mucinous neoplasm.

problems derived from the complete loss of pancreatic functions. Crippa et al[33] warned about the risk of overtreatment, including total pancreatectomy, in patients with preoperative morphologic diagnosis of combined/MD-IPMNs. Therefore, exact margin examination, rather than aggressive total pancreatectomy, is necessary to be performed.

To the best of our knowledge, our study is the first report that describes the application of IOP even in laparoscopic PD for the management of pancreatic head IPMNs. It remains debatable whether laparoscopic PD is a safe procedure,[34,35] however, currently published studies in the literature suggested that laparoscopic PD can play some role in the treatment of benign and low-grade malignant pancreatic tumors.[35–37] Our study showed that IOP in laparoscopic PD can be easily applied for patients with pancreatic head IPMNs with inconclusive MPD involvement based on preoperative imaging findings. According to time period, the first 4 IOP were performed in 7 years and the other 11 in 3 years. This low procedure numbers at an initial time have been overcome by the accumulation of our experience and advancement of technique. IOP application is expected to implement in more cases over time.

The mean MPD size in the IOP group was 10.8 ± 5.9 mm in our study, suggesting that almost all cases of IPMNs with dilated pancreatic duct can be examined using 3-mm high-resolution pancreatoscope. Therefore, in case of MPD size larger than 5 mm that belongs one of the “high-risk stigmata”, IOP should be recommended to perform routinely to define proper surgical extent of resection. However, intraoperative interpretation needs to be careful because the normal appearance of pancreatic duct may not always be correlated with the absence of dysplasia.

Recurrence was noted in only 3 patients (10.7%) in the IOP group and in another 2 patients (6.2%) in the FSB group in follow up period. Pea et al. [38]classified three mechanisms of local progression of IPMN in remnant pancreas with targeted mutational analysis acquired from first and recurred lesions after completion pancreatectomy. The first mechanism explains R1 resection. This mechanism can be excluded in our concept because all patients achieved R0 resections. The second mechanism means genetically related lesions consisting intraductal or intra parenchymal metastases with genetic relationship between initial and recurred tumors. The last mechanism means genetically unrelated lesions. We had one patient with MD-IPMN in FSB group who received completion total pancreatectomy for local recurrence with separate development of pancreatic ductal adenocarcinoma in remnant pancreas. The histopathologic reports showed totally different patterns between first and recurred tissues. Thus, this FSB recurrence case suggested separate development in remnant pancreas.

The 5-year DFS rate were 82.7% and 91.5% in the IOP and FSB group, respectively and there was no significant difference in overall DFS rate between patients with IOP and FSB group ($p = 0.225$). DFS rate in our study seems relatively higher than that ever reported.[4,19] However, this result could be explained that final pathologic report of most patients (71%) was benign or non-invasive carcinoma. Marchegiani et al[17] showed the recurrence of non-invasive IPMNs was only 9%, whereas invasive IPMNs recurred in 45% of cases. Moreover, the short follow up period might be another reason for this result. In our study, the median follow-up duration for all patients was 55.3 months, especially the IOP group was only 39.5 months (range, 8.9–135.6). Sho et al[20] analyzed the recurrence pattern after resection of IPMNs and reported that IPMNs can recur in the remnant pancreas even at 5 years after surgery, result of multicentric or metachronous oncogenesis of IPMNs. Therefore, long-term follow-up is needed to assure good prognosis of resected IPMNs in further study. On the other hand, this low tumor recurrence rate might be related with effort to achieve R0 resection using IOP and frozen section biopsy. Accurate intraoperative information on MPD in IPMNs will positively affect the surgical extent and even long-term oncologic outcomes.

There is one major concern for using IOP such as spillage problem. These authors experienced one case of mucinous seeding recurrence in the perihepatic space suggesting pattern as pseudomyxoma peritonnei in the IOP group. The patient got HIPEC (Hyperthermic intraperitoneal chemotherapy) surgery, and no

additional recurrence has been observed. Considering this recurrence pattern, surgeons should remind preventing intraperitoneal seeding by blocking spillage from main lesion. This team carefully use surgical stapler for pancreatic division preventing pancreatic juice spillage. Furthermore, this center has a strict principle that if the patient's preoperative image study shows mural nodule and irregularity around main pancreas lesion, IOP use should be prohibited before removing all potential lesions by endo-GIA application. Consequently, even though IOP can be done with carefully selected patients for reliability of the surgery, further study should be done to establish the meaning of performing this procedure.

There are several limitations in this study. First, it was a retrospective study in a single center. A selection bias could be present. Second, the small sample size is also limited. Third, in considering the nature of IPMNs, the follow up duration for the IOP group is definitely short to make long term oncologic outcomes. This issue should be further validated by multicenter studies, which can increase the sample size as well as the power of studies.

In conclusion, IOP can be safely performed in patients with pancreatic head IPMNs with MPD dilatation, even in the laparoscopic approach. This might be beneficial for determining an optimal surgical margin in well-selected cases. Further studies evaluating the long-term oncologic effect of IOP for the management of IPMNs are required.

Funding

Non declared.

Declaration of competing interest

Non declared.

Acknowledgments

This research was supported by a grant from the National Research Foundation (NRF-2016K1A3A1A12953723), and the part of results were presented under the title, “Image-guided Laparoscopic Pancreaticoduodenectomy”, in video symposium 4: Laparoscopic and Robotic Surgery for Pancreatic Disease, the 30th Meeting of Japanese Society of the Hepato-Biliary-Pancreatic Surgery (JSHBPS) held in Yokohama on June 9, 2018. Moreover, the authors would like to thank Dong-Su Jang, MFA (medical illustrator), for his help with the illustrations.

References

1. de Oliveira PB, Puchnick A, Szejnfeld J, Goldman SM. Prevalence of incidental pancreatic cysts on 3 tesla magnetic resonance. *PLoS One*. 2015;10(3), e0121317.
2. Sey MS, Teagarden S, Settles D, et al. Prospective cross-sectional study of the prevalence of incidental pancreatic cysts during routine outpatient endoscopic ultrasound. *Pancreas*. 2015;44(7):1130–1133.
3. Crippa S, Fernandez-Del Castillo C, Salvia R, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. *Clin Gastroenterol Hepatol*. 2010;8(2):213–219.
4. D'Angelica M, Brennan MF, Suriawinata AA, Klimstra D, Conlon KC. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg*. 2004;239(3):400–408.
5. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738–753.
6. Sauvanet A, Couvelard A, Belghiti J. Role of frozen section assessment for intraductal papillary and mucinous tumor of the pancreas. *World J Gastrointest Surg*. 2010;2(10):352–358.
7. Ito T, Doi R, Yoshizawa A, et al. The distribution of atypical epithelium in main-duct type intraductal papillary mucinous neoplasms of the pancreas. *J Hepatobiliary Pancreat Sci*. 2011;18(2):241–246. ; discussion 246-249.
8. Eguchi H, Ishikawa O, Ohigashi H, et al. Role of intraoperative cytology combined with histology in detecting continuous and skip type intraductal cancer existence for intraductal papillary mucinous carcinoma of the pancreas. *Cancer*. 2006;107(11):2567–2575.
9. Quentin V, Rioux-Leclercq N, Pagenault M, et al. Accuracy of preoperative imaging methods in a retrospective series of 14 patients with operated intraductal papillary mucinous tumors of the pancreas. *Gastroenterol Clin Biol*. 2005;29(2):150–155.
10. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology*. 2002;122(1):34–43.
11. Nagayoshi Y, Aso T, Ohtsuka T, et al. Peroral pancreatoscopy using the SpyGlass system for the assessment of intraductal papillary mucinous neoplasm of the pancreas. *J Hepatobiliary Pancreat Sci*. 2014;21(6):410–417.
12. Ohtsuka T, Gotoh Y, Nakashima Y, et al. Role of SpyGlass-DS(tm) in the preoperative assessment of pancreatic intraductal papillary mucinous neoplasm involving the main pancreatic duct. *Pancreatology*. 2018;18(5):566–571.
13. Cheon YK, Cho YD, Jeon SR, et al. Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. *Am J Gastroenterol*. 2010;105(9):1963–1969.
14. Mori Y, Ohtsuka T, Tamura K, et al. Intraoperative irrigation cytology of the remnant pancreas to detect remnant distinct pancreatic ductal adenocarcinoma in patients with intraductal papillary mucinous neoplasm undergoing partial pancreatectomy. *Surgery*. 2014;155(1):67–73.
15. Couvelard A, Sauvanet A, Kianmanesh R, et al. Frozen sectioning of the pancreatic cut surface during resection of intraductal papillary mucinous neoplasms of the pancreas is useful and reliable: a prospective evaluation. *Ann Surg*. 2005;242(6):774–778. discussion 778-780.
16. Gigot JF, Deprez P, Sempoux C, et al. Surgical management of intraductal papillary mucinous tumors of the pancreas: the role of routine frozen section of the surgical margin, intraoperative endoscopic staged biopsies of the Wirsung duct, and pancreaticogastric anastomosis. *Arch Surg*. 2001;136(11):1256–1262.
17. Marchegiani G, Mino-Kenudson M, Ferrone CR, et al. Patterns of recurrence after resection of IPMN: who, when, and how? *Ann Surg*. 2015;262(6):1108–1114.
18. Passot G, Lebeau R, Hervieu V, Ponchon T, Pilleul F, Adham M. Recurrences after surgical resection of intraductal papillary mucinous neoplasm of the pancreas: a single-center study of recurrence predictive factors. *Pancreas*. 2012;41(1):137–141.
19. Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology*. 2002;123(5):1500–1507.
20. Sho M, Nakajima Y, Kanehiro H, et al. Pattern of recurrence after resection for intraductal papillary mucinous tumors of the pancreas. *World J Surg*. 1998;22(8):874–878.
21. Fujita N, Aishima S, Iguchi T, et al. Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma. *Hum Pathol*. 2011;42(10):1531–1538.
22. Yelamali A, Mansard MJ, Dama R, Rebela P, Rao GV, Reddy DN. Intraoperative pancreatoscopy with narrow band imaging: a novel method for assessment of resection margins in case of intraductal papillary mucinous neoplasm. *Surg Endosc*. 2012;26(12):3682–3685.
23. Pucci MJ, Johnson CM, Punja VP, et al. Intraoperative pancreatoscopy: a valuable tool for pancreatic surgeons? *J Gastrointest Surg*. 2014;18(6):1100–1107.
24. Navez J, Hubert C, Gigot JF, et al. Impact of intraoperative pancreatoscopy with intraductal biopsies on surgical management of intraductal papillary mucinous neoplasm of the pancreas. *J Am Coll Surg*. 2015;221(5):982–987.
25. Navarro JG, Kang CM. Pitfalls for laparoscopic pancreaticoduodenectomy: need for a stepwise approach. *Ann Gastroenterol Surg*. 2019;3(3):254–268.
26. Han SH, Kang CM, Hwang HK, Yoon DS, Lee WJ. The Yonsei experience of 104 laparoscopic pancreaticoduodenectomies: a propensity score-matched analysis with open pancreaticoduodenectomy. *Surg Endosc*. 2020;34(4):1658–1664.
27. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery*. 2017;161(3):584–591.
28. Marchegiani G, Mino-Kenudson M, Sahora K, et al. IPMN involving the main pancreatic duct: biology, epidemiology, and long-term outcomes following resection. *Ann Surg*. 2015;261(5):976–983.
29. Crippa S, Tamburrino D, Partelli S, et al. Total pancreatectomy: indications, different timing, and perioperative and long-term outcomes. *Surgery*. 2011;149(1):79–86.
30. Matthaei H, Norris AL, Tsiatis AC, et al. Clinicopathological characteristics and molecular analyses of multifocal intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg*. 2012;255(2):326–333.
31. Inagaki M, Obara M, Kino S, et al. Pylorus-preserving total pancreatectomy for an intraductal papillary-mucinous neoplasm of the pancreas. *J Hepatobiliary Pancreat Surg*. 2007;14(3):264–269.
32. Yamaguchi K, Konomi H, Kobayashi K, et al. Total pancreatectomy for intraductal papillary-mucinous tumor of the pancreas: reappraisal of total pancreatectomy. *Hepato-Gastroenterology*. 2005;52(65):1585–1590.
33. Crippa S, Pergolini I, Rubini C, et al. Risk of misdiagnosis and overtreatment in patients with main pancreatic duct dilatation and suspected combined/main-duct intraductal papillary mucinous neoplasms. *Surgery*. 2016;159(4):1041–1049.
34. Zhang H, Wu X, Zhu F, et al. Systematic review and meta-analysis of minimally invasive versus open approach for pancreaticoduodenectomy. *Surg Endosc*.

2016;30(12):5173–5184.
35. Boggi U, Amorese G, Vistoli F, et al. Laparoscopic pancreaticoduodenectomy: a systematic literature review. *Surg Endosc*. 2015;29(1):9–23.
36. Umemura A, Nitta H, Takahara T, Hasegawa Y, Sasaki A. Current status of laparoscopic pancreaticoduodenectomy and pancreatectomy. *Asian J Surg*. 2018;41(2):106–114.
37. Soh YF, Kow AW, Wong KY, et al. Perioperative outcomes of laparoscopic and open distal pancreatectomy: our institution's 5-year experience. *Asian J Surg*. 2012;35(1):29–36.
38. Pea A, Yu J, Rezaee N, et al. Targeted DNA sequencing reveals patterns of local progression in the pancreatic remnant following resection of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. *Ann Surg*. 2017;266(1):133–141.