
Impact of Intraoperative Pancreatoscopy with Intraductal Biopsies on Surgical Management of Intraductal Papillary Mucinous Neoplasm of the Pancreas



Julie Navez, MD, Catherine Hubert, MD, Jean-François Gigot, MD, PhD, Ivan Borbath, MD, PhD, Laurence Annet, MD, PhD, Christine Sempoux, MD, PhD, Valérie Lannoy, MSc, Pierre Deprez, MD, PhD, Nicolas Jabbour, MD, FACS

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- BACKGROUND:** Because of its known malignant potential, precise histologic diagnosis of intraductal papillary mucinous neoplasm of the pancreas (IPMN) during intraoperative pancreatoscopy (IOP) is essential for complete surgical resection. The impact of IOP on perioperative IPMN patient management was reviewed over 20 years of practice at Cliniques universitaires Saint-Luc, Brussels, Belgium.
- STUDY DESIGN:** Among 86 IPMN patients treated by pancreatectomy between 1991 and 2013, 21 patients had a dilated main pancreatic duct enabling IOP and were retrospectively reviewed. The IOP was performed using an ultrathin flexible endoscope and biopsy forceps, and specimens of all suspicious lesions underwent frozen section examination.
- RESULTS:** Complete IOP with intraductal biopsies was easily and safely performed in 21 patients, revealing 8 occult IPMN lesions. In 5 cases (23.8%), initially planned surgical resection was modified secondary to IOP: 3 for carcinoma in situ and 2 for invasive carcinoma. The postoperative morbidity rate at 3 months was 25.0% (5 of 20); 1 patient died from septic shock postoperatively and was excluded. Median follow-up was 93 months (range 13 to 248 months). Nineteen of 21 patients were still alive and free of disease at last follow-up (90.5%); there was 1 patient with invasive carcinoma at initial pathology (pT3 N1) who died of pulmonary recurrence 21 months after surgery.
- CONCLUSIONS:** Intraoperative pancreatoscopy of the main pancreatic duct combined with intraductal biopsies plays a significant role in the surgical management of IPMN patients and should be used in all patients presenting a sufficiently dilated main pancreatic duct. (J Am Coll Surg 2015;221:982–987. © 2015 by the American College of Surgeons)
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Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are increasingly diagnosed tumors that are often asymptomatic in their first stages and are characterized by

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Received June 15, 2015; Revised July 19, 2015; Accepted July 27, 2015. From the Unit of Hepato-biliary and Pancreatic Surgery, Department of Abdominal Surgery and Transplantation (Navez, Hubert, Gigot, Jabbour), the Departments of Hepato-Gastro-Enterology (Borbath, Deprez), Imaging study (Annet), and Pathology (Sempoux), and the Cancer Center Institute Roi Albert II (Lannoy), Cliniques universitaires Saint-Luc, Université catholique de Louvain (UCL), Brussels, Belgium.

Correspondence address: Nicolas Jabbour, MD, FACS, Department of Abdominal Surgery and Transplantation, Cliniques universitaires Saint-Luc, Avenue Hippocrate, 10, 1200 Brussels – Belgium. email: nicolas.jabbour@uclouvain.be

papillary proliferations of mucin-producing ductal epithelium, leading to dilatation of the main pancreatic duct or its sub-branches. The overall incidence of IPMN is difficult to assess, but with increased routine use of computed tomography and magnetic resonance imaging, diagnosis of asymptomatic cystic lesions of the pancreas was recently observed to be more than 4%, half of which were neoplastic; IPMN constituted 40% of these, so the incidence of IPMN incidence was about 0.8%.¹ The IPMN spreads longitudinally along the ducts and has a significant potential for malignant transformation, with the presence on biopsy of diffuse or multifocal high grade dysplasia ranging from 7% to 54%.²⁻⁷ Pancreatic IPMNs are classified, based on imaging, into main-duct (MD), branch-duct (BD), or mixed subtypes, depending on the involvement of the ductal system.⁸ Prognosis depends on the presence or absence of invasive

Abbreviations and Acronyms

BD	= branch duct
CT	= computed tomodensitometry
EUS	= endoscopic ultrasonography
IPMN	= intraductal papillary mucinous neoplasm
IOP	= intraoperative pancreatoscopy
MD	= main duct
MRCP	= magnetic resonance cholangiopancreatography
POP	= peroral pancreatoscopy

carcinoma, reported to occur in around 70% of MD-IPMN.⁹

Preoperative investigations include computed tomodesitometry (CT), ERCP, endoscopic ultrasonography (EUS), and/or magnetic resonance cholangiopancreatography (MRCP). These routine imaging technologies help to distinguish IPMN from other cystic lesions of the pancreas, but cannot reliably differentiate benign from malignant disease. Preoperative peroral pancreatoscopy (POP) is not considered routine imaging because it is technically difficult; however, it does enable direct observation and biopsy sampling of the ductal epithelium. Intraoperative pancreatoscopy (IOP) was first described in 1998 by Kaneko and colleagues, who found the technique safe, effective, and easily performed.¹⁰ There have been only rare reports evaluating the usefulness of IOP for IPMN. Because of the potential malignant growth, complete resection of IPMN lesions is essential and requires precise diagnosis of the extent of the disease. In a previous study, we reported our clinical experience with surgical management of IPMN, highlighting the importance of intraoperative ultrasound, frozen sections of the surgical margins, and perioperative endoscopic examination of the main pancreatic duct with staged biopsies.¹¹ This study's objective was to report our experience with using IOP with intraductal biopsies for IPMN of the pancreas and the impact of IOP on the perioperative therapeutic decision.

METHODS

From December 1991 to March 2014, 86 consecutive patients with IPMN of the pancreas were treated by surgical pancreatic resection at Cliniques universitaires Saint-Luc, Brussels, Belgium, and were retrospectively reviewed. Operative risk and comorbidities were evaluated according to the American Society of Anesthesiology (ASA) physical score.¹²

Diagnosis of IPMN was based on imaging, endoscopy, and pathologic examination including cytology and

histopathology. Preoperative assessment was made by CT, MRCP, and EUS, with histopathologic examination of pancreatic fluid or biopsies of suspicious lesions. Five patients had a preoperative POP.

Indications for surgery were defined according to the International Consensus Guidelines for Management of IPMN in 2006, reporting that all MD tumors should be resected, while only BD tumors > 3 cm, symptoms, and/or high risk stigmata should need a surgical resection (Sendai criteria).¹³ For patients treated before 2006, indications for surgery were IPMN with symptoms or suspicion of malignancy.

Only IPMN classified as MD subtype (37 patients) and mixed subtype (33 patients) were considered. The 16 remaining IPMN were of the BD subtype. Selection of patients for IOP was based on the main pancreatic duct diameter within the pancreatic remnant being wider than 5 mm to enable introduction of a flexible endoscope. Among patients with a dilated main pancreatic duct ($n = 70$), IOP could be performed in only 21 patients (30.0%). In the 49 patients not included, 43 had a main pancreatic duct within the pancreatic remnant that was not wide enough, 2 had a total pancreatectomy as planned after preoperative assessment, 3 had a total pancreatectomy after positive frozen sections, and 1 could not support a total pancreatectomy despite positive frozen sections.

At frozen section and final pathology of surgical and intraductal specimens, low and moderate grade dysplasia were considered benign, and high grade dysplasia, carcinoma in situ, and invasive carcinoma were considered malignant; carcinomas were classified according to the WHO classification system.¹⁴ For patients treated before 1996 (before inclusion of the concept of IPMN), pathology was reviewed and reassessed.

Technique

At exploration under laparoscopy ($n = 1$) or laparotomy ($n = 20$), the pancreatic lesion was explored and located precisely, using intraoperative ultrasonography, to define surgical margins. After transection of the pancreas, exploration of the main pancreatic duct was performed on the remaining pancreas with an ultrathin flexible endoscope (external diameter of 3.3 mm or 4.9 mm, Olympus). Pathognomonic lesions of IPMN, such as papillary protrusions, fish-egg-like protrusions, and other atypical lesions, were carefully sought. Biopsy forceps were used through the operative channel to perform intraductal biopsies, which were analyzed by frozen section. Extent of resection was determined by paying careful attention to preoperative investigations, to frozen sections of the surgical margins, and to IOP.

Surgical complications were graded according to the Clavien-Dindo classification.¹⁵

All patients had long-term follow-up with clinical, biologic (including tumor markers), endoscopic, and radiologic assessment, including MRCP. When recurrence was suspected, PET-CT was performed. All data were expressed as median with range.

RESULTS

Intraoperative pancreatoscopy of the main pancreatic duct was performed safely and easily in 21 patients during pancreatectomy (Fig. 1). There were 13 men and 8 women, with a median age at surgery of 62 years (range 34 to 73 years) (Table 1). All patients were American Society of Anesthesiologists 2. At diagnosis, acute pancreatitis was present in 47.6% of patients, weight loss in 28.6%, isolated abdominal pain in 28.6%, and steatorrhea in 23.8%; 14.3% of patients had no symptoms. Median time from symptoms to surgery was 13.5 months (range 1 to 192 months). Preoperative pancreatoscopy was performed in 5 patients.

Pancreatoduodenectomy was performed in 17 patients (1 with additional segmental excision of the tail for a skipped lesion), total pancreatectomy in 3 patients, and a distal pancreatectomy in 1 patient (Table 2). The median diameter of the main pancreatic duct was 8 mm (range 5 to 12 mm). Median hospital stay was 25 days (range 8 to 65 days). In this series, 1 patient died from septic shock after pulmonary atelectasis, pleural effusion, and retrogastric collection after 65 days. The mortality rate within 3 months was 4.8% (1 of 21). Among the surviving patients, the postoperative morbidity rate with a Clavien-Dindo score greater than II at 3 months was 25.0%

Table 1. Demographic Data

Baseline characteristic	Data
n	21
Age at diagnosis, y, median (range)	62 (34–73)
Sex, n (%)	
Female	13 (62)
Male	8 (38)
Clinical presentation, n (%)	
Acute pancreatitis	10 (48)
Weight loss	6 (29)
Abdominal pain	6 (29)
Steatorrhea	5 (24)
Diabetes	3 (14)
Cholangitis	1 (5)
No symptoms	3 (14)
Time from initial symptoms to surgery, mo, median (range)	13.5 (1–192)

(5 of 20), including severe pancreatic fistula causing intraperitoneal hemorrhage (n = 1), intraperitoneal collection (n = 3), evisceration (n = 1), and hepatic artery aneurysm (n = 1, comorbidity: intraperitoneal collection). No complication related to IOP, such as intraductal bleeding, was encountered.

The IOP revealed 8 cases of occult IPMN lesions, undetected by preoperative assessment. Endoscopic findings included papillary protrusions in 3 patients, fish-egg–like protrusions in 2 patients, and atypical lesions in 3 patients (Table 3). All 8 patients underwent preoperative EUS and MRCP except 1 patient, who had abdominal CT instead of MRCP (Patient No. 1, Table 3).

Initially planned surgical resection was modified secondary to IOP and intraductal biopsies for 5 of the 21

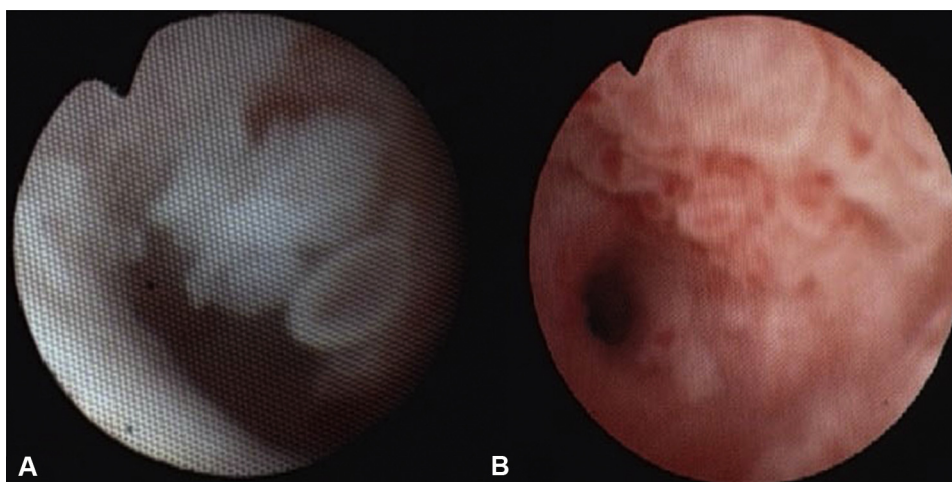


Figure 1. Intraoperative endoscopic examination of the main pancreatic duct after transection of the pancreas. (A) Papillary projections. (B) Fish-egg–like protrusions.

Table 2. Postoperative Data

Postoperative characteristic	Data
Hospital stay, d, median (range)	25 (8–65)
Morbidity (Dindo-Clavien \geq III), n (%)	
Grade III	3 (14)
Grade IV	2 (10)
Postoperative mortality, n (%)	1 (5)
Median follow-up, m, median (range)	93 (13–248)

patients (23.8%). Indeed, among these patients, at final pathology, 3 had carcinoma in situ, and 2 had invasive carcinoma. Frozen section examination and diagnosis of intraductal biopsies was confirmed at final pathology. In 1 patient, pancreatoduodenectomy was completed by distal pancreatectomy, leaving the pancreatic body in place. In a second patient, the distal splenopancreatectomy initially planned needed to be converted into a pancreatoduodenectomy after identification of adenocarcinoma in the head of the pancreas at final pathology. In a third patient, the type of resection had to be defined after the pancreatoscopy because the preoperative diagnosis could not specify the precise location of the lesion. For the 2 remaining patients, pancreatic resection had to be totalized.

Among the 5 patients who underwent a preoperative peroral pancreatoscopy, papillary proliferations were observed in all patients; 1 had invasive carcinoma at biopsy. Premalignant and malignant IPMN lesions were confirmed in 2 patients at frozen section of the intraductal biopsy during IOP, at locations outside the planned surgical resection. In the 3 other patients, lesions were included in the planned resected surgical specimen. At final pathology, each patient had carcinoma in situ in surgical specimens.

Median follow-up was 93 months (range 13 to 248 months). Nineteen of 21 patients were still alive and free of disease at last follow-up (90.5%). Only 1 patient

with invasive carcinoma and lymph node involvement at initial pathology (pT3 N1) had malignant recurrence in the lungs and died 21 months after surgery. No patient with normal IOP and/or low grade dysplasia at frozen section examination has suffered from a recurrence from malignant disease at the time of writing. Three patients had benign recurrences of their disease at radiologic and/or endoscopic assessment after 16, 35, and 60 months; pathology at the time of initial pancreatic surgery showed no dysplasia in 1 and carcinoma in situ in 2. No recurrence was seen at PET-CT. The 3 patients were followed with biannual tumor markers, annual MRCP, and EUS combined with cytology every 2 years; last follow-ups were at 113, 132, and 112 months, respectively. At the time of writing, these patients appear to be free of disease and have not required any adjuvant treatment.

DISCUSSION

Intraductal papillary mucinous neoplasms of the pancreas are potentially malignant lesions ranging from dysplasia to invasive carcinoma. Identification of malignancy is challenging, despite continuous progress of preoperative investigation techniques. Intraoperative pancreatoscopy of the main pancreatic duct along with frozen section examinations of intraductal biopsies and surgical margins appear decisive for establishing IPMN extent and for adapting the operative strategy. This intraoperative procedure also enables detection of missed lesions in patients with multicentric disease responsible for neoplastic recurrences despite negative resection margins. In our series of 21 patients, IOP and frozen section modified operative strategy in 5 patients with carcinoma (invasive or not), and only 1 patient suffered a malignant recurrence (the only one with lymph node involvement observed at initial operation).

Feasibility and safety of IOP have both been demonstrated in several studies. Kaneko and colleagues¹⁰

Table 3. Impact of Abnormal Findings at Intraoperative Pancreatoscopy on Surgical Management of Intraductal Papillary Mucinous Neoplasm (8 of 21 Patients)

Patient No.	Initial surgery	Plan modified by IOP	Final surgery	Occult lesion at IOP	FS biopsy	Final pathology	Recurrence	Follow-up, mo
1	PD	No	PD	Papillary protrusion	B	B	No	248
2	PD	No	PD	Papillary protrusion	B	B	No	129
3	PD	No	PD	Fish-eggs like	LGD	T _{is} N0	NA	2
4	PD	Yes	PD + DP	Atypical lesion, lithiasis	NA	T1 N0	No	127
5	DP	Yes	PD	Fish-eggs like	ADK	T _{is} N0	Yes (B)	132
6	UK	Yes	PD	Papillary protrusion	LGD	T _{is} N0	Yes (B)	113
7	DP	Yes	TP	Atypical lesion	HGD	T3 N1	Yes (M)	21
8	PD	Yes	TP	Atypical lesion	HGD	T3 N0	No	65

ADK, adenocarcinoma; B, benign; DP, distal pancreatectomy; FS, frozen section; HGD, high grade dysplasia; IOP, intraoperative pancreatoscopy; LGD, low grade dysplasia; NA, not addressed; PD, pancreatoduodenectomy; TP, total pancreatectomy; UK, unknown.

evaluated the accuracy of IOP in diagnosing IPMN lesions in a series of 24 patients, identifying lesions undetected preoperatively in 10 patients, 3 of them requiring additional pancreatic resection. Yelamali and associates¹⁶ described 1 case of IOP with narrow band imaging providing excellent image quality, enabling total clearance of the disease. Recently, Pucci and colleagues¹⁷ published their experience of 23 cases using IOP during pancreatic surgery, including 18 cases of IPMN. In 5 patients (5 of 18, 27.8%), surgical resection was extended secondary to intraoperative endoscopic findings.

Preoperative peroral pancreatoscopy has been reported to enable preoperative exploration of the pancreatic duct. Hara and colleagues¹⁸ described a large series of 60 patients who underwent POP for IPMN, combined with intraductal ultrasonography in 40 of them. A sensitivity of 100% was achieved in differentiating benign from malignant MD- subtype IPMN. These authors concluded that combining these 2 techniques improved differential diagnosis between malignant and benign IPMN and led to more precise resection. A workgroup of experts recently established consensus statements regarding the usefulness of POP, one of whom specifically stated, "In patients with main duct IPMN, POP may be used to assess extent of tumor to assist surgical resection (recommendation grade C)."¹⁹ However, POP remains technically difficult and requires great endoscopic ability and experience. The device is fragile, and acute angulation at insertion of the endoscope can damage it. Moreover, sphincterotomy must be performed to pass the papilla, and it carries an increased risk of acute pancreatitis, further increased by intraductal debris. Intraoperative pancreatoscopy bypasses each of these difficulties. Advantages of intraoperative pancreatoscopy are direct access to the pancreatic duct after transection of the pancreas, immediate visualization, and easier maneuverability of the thin flexible endoscope. Moreover, endoscopic examination and surgical resection are performed by a single person during the same procedure, which enables location of an optimal transection line during pancreatectomy. No complication of IOP, such as intraductal bleeding, was observed in our series, as in other published series on IOP.^{10,17} Furthermore, the risk of intraductal bleeding is very small given that the endoscopic biopsy forceps take very small samples (<1 mm).

The role of frozen section examinations during pancreatic resection has been clearly demonstrated previously. Paye and associates²⁰ showed, in their series of 41 patients, that diagnostic accuracy of frozen section histologic examination of pancreatic resection margins was 92%, ensuring complete resection of IPMN. Couvelard and colleagues²¹

reported that frozen section examinations changed the extent of resection in 30% of patients and enabled complete resection in 97% of patients. In our previous report, Gigot and associates¹¹ confirmed these results and concluded that routine frozen section pathologic examination of surgical margins, endoscopic examination of the main pancreatic duct, and biopsies in particular should be used to delineate the extent of IPMN. In this study, frozen sections of the surgical margins and endoscopic biopsies were positive for malignancy in 2 cases and 3 cases, respectively (5 of 21, 23.8%), justifying the extensive pancreatic resection. Pathologic examination of frozen sections is essential and decisive to help establish resection limits and avoid performing a systematic total pancreatectomy.

Prognosis of noninvasive carcinoma in IPMN is favorable when resected, with 5-year survival rates after surgery varying from 90% to 100%.^{7,22} And it is well known now that the malignant potential in case of a dilated main duct ranges from 60% to 92%.⁶ The contribution of IOP could therefore be crucial to detect premalignant or malignant lesions undetectable preoperatively. However, in the case of mixed subtype IPMN, lesions of the pancreatic branch ducts cannot be visualized because the endoscope can only be introduced into the main pancreatic duct. The low rate of malignant recurrence in this study could possibly be due to complete resection at the time of surgery, including occult lesions. Kaneko and colleagues¹⁰ confirmed the potential of IOP to decrease malignant recurrence within 4 years' follow-up time. Although the small sample size over 23 years did not allow comparative series in this study, the sample is equal or superior to that of the few published studies on IOP.

CONCLUSIONS

Intraoperative pancreatoscopy of the main pancreatic duct combined with frozen section examination of intraductal biopsies should play a significant role in the surgical management of patients with IPMN of the pancreas and should be used in all patients with a sufficiently dilated pancreatic duct.

Author Contributions

Study conception and design: Navez, Gigot, Lannoy, Jabbour
Acquisition of data: Navez, Hubert, Gigot, Annet, Sempoux, Deprez, Lannoy
Analysis and interpretation of data: Navez, Gigot, Jabbour
Drafting of manuscript: Navez, Gigot, Lannoy, Jabbour
Critical revision: Gigot, Borbath, Jabbour

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