J Hepatobiliary Pancreat Sci (2010) 17:516–522
DOI 10.1007/s00534-009-0257-5

ORIGINAL ARTICLE

The distance of tumor spread in the main pancreatic duct of an intraductal papillary-mucinous neoplasm: where to resect and how to predict it

Ken-ichi Okada · Toshihide Imaizumi · Kenichi Hirabayashi · Masahiro Matsuyama · Naoki Yazawa · Shoichi Dowaki · Kosuke Tobita · Yasuo Ohtani · Yoshiaki Kawaguchi · Makiko Tanaka · Sadaki Inokuchi · Hiroyasu Makuuchi

Received: 24 August 2009 / Accepted: 8 December 2009 / Published online: 3 February 2010

Abstract
Background The surgical decision regarding where to resect the pancreas is an important judgement that is directly linked to the surgical procedure. An appropriate surgical margin to resect intraductal papillary-mucinous neoplasm (IPMN) of the pancreas based on the distance of tumor spread (DTS) in the main pancreatic duct has not been adequately documented. We analyzed the appropriate surgical margin based on the DTS in the main pancreatic duct of IPMN and the positive rate at the pancreatic cut end margin.
Methods Forty patients with main duct- or mixed-type IPMN diagnosed histopathologically who underwent surgery at Tokai University Hospital between 1991 and 2008 were retrospectively analyzed. The resection line was determined to achieve a 2-cm surgical margin in patients with main duct- or mixed-type IPMN and as limited a resection as possible to remove the dilated branch duct in patients with branch duct-type IPMN according to macroscopic type. The dysplastic state of the epithelium was judged as positive for carcinoma in situ (high-grade dysplasia) or adenoma (very low to moderate dysplasia) and judged as negative for hyperplasia or normal.
Results The mean DTS in the main pancreatic duct was 41.6 ± 30.0 mm, and that of the distance of tumor absence was 13.6 ± 12.4 mm. The positive rate at the pancreatic cut end margin in frozen sections was 29.7%. The final positive rate at the pancreatic cut end margin was 26.2%. There has been no evidence of local recurrence in the remnant pancreas. DTS in the main pancreatic duct of IPMN was correlated with the maximum diameter of the duct ($R = 0.678$).
Conclusion Distance of tumor spread offered important insights about the appropriate site to resect the pancreas and the positive rate at the cut end margin in IPMN.

Keywords Intraductal papillary-mucinous neoplasm · Distance of tumor spread · Main pancreatic duct · Maximum diameter

K. Okada (✉) · T. Imaizumi · M. Matsuyama · N. Yazawa · S. Dowaki · K. Tobita · Y. Ohtani · H. Makuuchi
Department of Surgery, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan
e-mail: okada@is.icc.u-tokai.ac.jp

K. Hirabayashi
Department of Pathology, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan

Y. Kawaguchi
Department of Medicine, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan

M. Tanaka · S. Inokuchi
Department of Critical Care and Emergency Medicine, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan

Introduction

There are few current topics in pancreatic surgery that are more fascinating than the management of intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas. The extent of pancreatic resection depends on the level of ductal tumor involvement, as assessed by preoperative imaging studies and intraoperative ultrasonography. In addition, the pancreatic duct margin should be confirmed as tumor-free by frozen section histopathology. Regardless of whether IPMNs involve the main pancreatic duct, surgical management must ideally involve the complete resection of the potentially malignant lesion. Because extension along

the pancreatic duct may be difficult to determine preoperatively, the planned resection could be modified based on intraoperative frozen section analysis [1–3]. This therapeutic strategy appears to be useful in IPMNs involving the main pancreatic duct because most of these lesions show a contiguous pattern. There have been few reports on the appropriate position to resect IPMN of the pancreas. The surgical decision regarding where to resect the pancreas is an important judgement that is directly linked to the surgical procedure. Recently, various operative procedures such as total pancreatectomy for the main duct-type of IPMN or pancreas-preserving segmental pancreatectomy have been accepted throughout the world based on the clinicopathological analyses or long-term results of IPMN treatment [4–8]. Clinically, it is often difficult to make a decision regarding where to resect, especially in main duct- and mixed-type lesions with diffuse or focal main pancreatic duct dilatation. We introduced a new concept: "the distance of tumor spread in the main pancreatic duct of IPMN." Main duct-type IPMN is frequently malignant and requires careful evaluation in regard to indications for surgery, as well as the appropriate area and extent of resection [9–11]. Intraoperative ultrasonography and pancreatoscopy may be helpful in determining the site of resection. However, there may exist a discrepancy between the dilated ductal segment and the actual localization of IPMN cells [8], and the IPMN may still affect the stump following resection.

Intraoperatively, frozen section diagnosis must be adequately applied, although a diagnosis based on frozen histology is not always accurate and definite in all ducts. Therefore, we focused on distance of tumor spread (DTS) only in the main duct in this article. We discussed an appropriate position to resect the pancreas based on the analysis of DTS in the main pancreatic duct of IPMN and the positive rate at the pancreatic cut end margin. Further, we examined the correlation between the maximum diameter of the main duct and DTS in the duct with the hypothesis that a large volume of mucus may be associated with DTS [9]. We seek to provide pancreatic surgeons with a guide for the determination of where to resect, particularly for main duct- and mixed-type IPMN, and how to predict it preoperatively based on imaging studies.

Patients and methods

Study population

All tissue specimens were obtained through the surgical resection of IPMNs. Forty patients with main duct- or mixed-type IPMN diagnosed histopathologically who underwent surgery at Tokai University Hospital between 1991 and 2008 were retrospectively analyzed. We reviewed data retrospectively with additional independent histopathologic confirmation. There were no operation-related deaths, and all patients underwent macroscopically curative resection without any residual tumor. Invasive IPMN could spread along the retroperitoneal tissue, but IPMNs are extensive tumors that usually spread along the ductal tree. Because of this, the present paper focused on IPMN involving the main duct excluding invasive and branch duct-type IPMN to solely investigate DTS in the main pancreatic duct. The patients comprised 29 men and 11 women, with a median age of 67 (44–81) years. The operative procedures included 15 pylorus-preserving pancreatoduodenectomies (PPPDs), 15 distal pancreatectomies (DPs), 6 median pancreatectomies (MPs), 3 total pancreatectomies (TPs), and 1 duodenal-preserving pancreas head resection (DPPHR).

Histological examination

Pancreatic tissue specimens for histological analysis were rapidly fixed in 10% buffered formalin for 24–48 h, routinely embedded in paraffin, and cut into serial 5-mm-thick slices. The presence of IPMNs was examined with 5-μm-thick sections stained with hematoxylin and eosin. After the histopathologic examination of all sections, lesions were classified as intraductal papillary-mucinous adenoma (IPMA), borderline IPMN, or noninvasive intraductal papillary-mucinous carcinoma (IPMC) according to the WHO classification. DTS in the main pancreatic duct (mpd+) was measured by macroscopic/microscopic histopathological examination in the pathologic specimens. The distance of tumor absence between the tips of the tumors and pancreatic cut end margin (mpd−) was measured in the same way. In cases presenting skip lesions, DTS was measured as the distance from the edge of the lesions to the opposite edge. When the specimens showed a positive margin, DTS was measured as the distance from the cut end margin to the tumor edge on the other side (DTS could not be accurately measured in this group). The dysplastic state of the epithelium in the main pancreatic duct was judged as positive for carcinoma in situ (CIS) (high-grade dysplasia) or adenoma (very low to moderate dysplasia) and judged as negative for hyperplasia or normal. Frozen sectioning was performed either using a resected specimen or a fresh slice of pancreatic cut surface harvested immediately after transaction. We analyzed DTS in the main pancreatic duct of IPMN and the positive rate in frozen sections including cases which finally underwent total pancreatectomy, but we excluded these cases from analysis of the positive rate of pancreatic cut end margins in the final diagnoses. In MP cases, the bilateral cut end margins were examined. We expressed cases of dysplastic

epithelium presenting main and side branch ductal involvement as pathologically mixed-type in this study.

Imaging studies

Determination of the position to resect the pancreas with IPMN. As a first step, abdominal ultrasonography (AUS) and abdominal computed tomography (CT) were used to evaluate the size, location, and number of lesions. Next, as the second step, the type of IPMN, diameter of the main pancreatic duct, nodules, and cytology were examined by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS). The third step comprised ERCP with peroral pancreatography (POPS) or intraductal ultrasonography (IDUS) to evaluate the distribution and extent of IPMN. Based on each of the findings, the resection line was empirically determined to achieve a 2-cm surgical margin from the tips of the intraductal tumors if the entire pancreatic duct was dilated or from the edge of the dilated main pancreatic duct on the preoperative image in patients preoperatively diagnosed (macroscopic type) with main duct- or mixed-type IPMN. On the other hand, patients diagnosed with branch duct-type IPMN (macroscopic type) underwent as limited a resection as possible to be able to remove the dilated branch duct completely in surgery.

The maximum diameter of the main pancreatic duct. The maximum diameter of the main pancreatic duct was alternatively measured by AUS or EUS for all cases preoperatively.

Selection of operative procedures

Based on the decision regarding where to resect the pancreas, basically, PPPD or DP was chosen when a greater pancreatic volume could be preserved in patients diagnosed with main duct- or mixed-type IPMN. In particular, main duct-type IPMN with diffuse main duct dilatation is a good indication for TP in such patients. MP was only performed in patients diagnosed preoperatively with branch duct-type IPMN in the pancreas body. Generally, patients with suspected invasive IPMC underwent treatment in the same way as conventional pancreatic ductal adenocarcinoma with dissection of group 1 lymph nodes and sampling of group 2 lymph nodes.

Intraoperative strategy for the resection line

Intraoperative ultrasonography was used appropriately to ensure the edge of the dilated main duct and decide on the resection line. Margins of resection were examined using frozen sections at the time of resection in patients with IPMNs. If IPMNs were present at the margin of resection, pathologists were requested to pay particular attention to the dysplastic state of the epithelium and the presence of main versus side branch ductal involvement. The presence of invasive cancer or CIS at the margin necessitated further resection of at least 2 cm. The presence of adenoma at the margin should prompt the surgeon to consider further resection, 1 cm usually, to achieve clear margins. Total pancreatectomy as a result of the presence of adenoma is usually avoided.

Statistical analysis

Descriptive statistics were employed to examine the demographic characteristics of the study population. Data are expressed as medians (25th and 75th percentiles) and mean ± SD. Statistical comparisons between two groups were made using the χ^2 test, or the Mann-Whitney *U*-test for nonparametric data. A P value <0.05 was considered to indicate significance. All analyses were performed using the statistical software package SPSS II (version 11.0; SPSS, Tokyo, Japan).

Results

Histopathologic evaluation of IPMN

The 40 IPMNs were classified into 16 IPMAs, 5 borderline IPMNs, and 19 noninvasive IPMCs according to the WHO classification. Compared with macroscopic type, 16 main duct-type, and 11 mixed-type IPMNs were confirmed as same type, but 13 branch duct-type IPMNs were diagnosed as pathologically mixed-type by histopathological examination. None of them exhibited an ovarian-like stroma, and all lesions showed communication with the pancreatic ductal system.

To evaluate IPMN extension, we examined DTS in the main pancreatic duct. Two cases showed skip lesions, and 38 IPMNs were continuous. The mean mpd+ was 41.6 ± 30.0 mm, and that of mpd− was 13.6 ± 12.4 mm. The mean mpd+ in main duct-type (66.0 ± 33.1 mm) was longer than that of pathologically mixed-type (38.1 ± 28.4 mm) IPMN ($P = 0.09$).

The positive rate of the pancreatic cut end margin was evaluated in 42 margins. Frozen sections were produced for 37 pancreatic cut end margins intraoperatively. The 37 frozen sections revealed that the main duct epithelium was normal ($n = 26$, 70.3%), or contained IPMA ($n = 10$, 27.0%) or noninvasive IPMC ($n = 1$, 2.7%) lesions. The branch duct epithelium was normal ($n = 35$, 94.6%), or contained IPMA ($n = 2$, 5.4%) in frozen sections. No frozen section revealed noninvasive or invasive carcinoma

of the branch duct. The positive rate at the pancreatic cut end margin in frozen sections was 29.7%. Additional resection of the positive margins was only performed in five cases due to the residual pancreatic volume or anatomical factors. The final diagnosis revealed that the main duct epithelium was normal ($n = 31$, 73.8%) or contained IPMA ($n = 10$, 23.8%) or noninvasive IPMC ($n = 1$, 2.4%) lesions. The branch duct epithelium was normal ($n = 38$, 90.5%) or contained IPMA ($n = 4$, 9.5%). No noninvasive nor invasive carcinoma was noted in the branch duct epithelium of the final cut end margin. The final positive rate of the pancreatic cut end margin was 26.2% (Table 1). One patient showing noninvasive carcinoma of both the frozen section and final cut end margin was overdiagnosed with invasive carcinoma and was positive for the dissected peripancreatic tissue margin intraoperatively; therefore, we did not perform additional resection. It was the only case of recurrence by peritoneal dissemination, and the patient has remained alive and free from disease for 3 years after reoperation of recurrent tumorectomy. Otherwise, there has been no evidence of local recurrence in the remnant pancreas or distant organ metastasis in this study.

Macroscopic type and operative procedures for the 40 IPMNs are shown in Table 2. (We performed DPPHR due to the status post esophagectomy with gastric tube reconstruction and advanced age in one patient.) Limited resection of the pancreas tended to be performed in patients diagnosed preoperatively with branch duct-type IPMN (MP 6 out of 13 cases, 46.2%) than those diagnosed preoperatively with the main duct- or mixed-type IPMN (DPPHR 1 out of 27 cases, 3.7%). The positive rate at the pancreatic cut end margin for the final diagnosis was relatively high in MP (3 out of 6 cases, 50.0%).

Predictor of the distance of tumor spread

The diameter of the main pancreatic duct evaluated by AUS or EUS revealed that the mean maximum diameter of the main pancreatic duct was 8 ± 5 mm and those of the main duct- and pathologically mixed-type IPMN were 14 ± 7 and 7 ± 4 mm, respectively. The two independent data points (the maximum diameter of the main pancreatic duct and DTS in the main pancreatic duct of IPMN, i.e., mpd+) were analyzed regarding the correlation between them. In our study, DTS in the main pancreatic duct of IPMN was correlated with the maximum diameter of the duct (Fig. 1, $R = 0.678$). Furthermore, IPMNs with a strongly dilated main pancreatic duct (maximum diameter $\geq$6 mm: mpd+ $\geq$40 mm, 15 cases; and mpd+ <40 mm, 9 cases) showed a significantly greater spreading distance than those with a less dilated main pancreatic duct (maximum diameter <6 mm: mpd+ $\geq$40 mm, 2 cases; and mpd+ <40 mm, 14 cases) ($P < 0.001$, Table 3).

Discussion

Intraductal papillary-mucinous neoplasms are a well-characterized group of intraductal mucin-producing cystic neoplasms of the pancreas with a clear malignant potential. IPMNs are extensive tumors that often spread along the ductal tree [12, 13]. The resection of IPMNs should be tailored based on longitudinal spreading into the pancreatic ductal system and the presence of malignant transformation. However, recent reports have discussed imaging studies, treatment strategies, surgical management, and intraoperative strategies for IPMN [1–3, 11, 14–17], but there has been no discussion on where to resect the pancreas based on an analysis of the extension or distribution of IPMNs. To our knowledge, no other study has simultaneously discussed the appropriate surgical margin and positive rate at the pancreatic cut end margin. We introduced a new concept: "the distance of tumor spread in the main pancreatic duct of IPMN" because it is a significant factor that could influence the surgical procedure itself. We also demonstrated that the maximum diameter of the main pancreatic duct is a predictor of DTS in the main duct of IPMN.

Main duct-type IPMN is frequently malignant and requires careful evaluation in regard to the presence of mural nodules, potential extraductal and extrapancreatic

Table 1 The positive rate at the pancreatic end margin and results of frozen sections

Status of main duct epithelium[a]	Main duct/mixed-type ($n = 37$): significant lesions at FS		Main duct/mixed-type ($n = 42$): significant lesions at final diagnosis	
	n (%)	Positive rate (%)	*n* (%)	Positive rate (%)
Normal-hyperplasia	26 (70.3)	29.7	31 (73.8)	26.2
Adenoma	10 (27.0)		10 (23.8)	
Noninvasive carcinoma	1 (2.7)		1 (2.4)	

FS Frozen section, *n* number of cut end margins

[a] Adenoma includes very low to moderate dysplasia. Noninvasive carcinoma means high-grade dysplasia (carcinoma in situ)

Table 2 Macroscopic type and operative procedures

Procedure (*n*)	Preoperative diagnosis for the type of IPMN (*n*)	Positive rate (%)
PPPD (15)	Main (4)	6.7
	Mixed (7)	
	Branch (4)	
DP (15)	Main (8)	26.7
	Mixed (4)	
	Branch (3)	
MP (6)	Branch (6)	50.0
DPPHR (1)	Main (1)	n.e.
TP (3)	Main (3)	n.e.

PPPD Pylorus-preserving pancreatoduodenectomy, *DP* distal pancreatectomy, *MP* median pancreatectomy, *DPPHR* duodenal-preserving pancreas head resection, *TP* total pancreatectomy, *n* number of cases, *positive rate* positive rate at final pancreatic cut end margin, *n.e.* not evaluated

One patient underwent DPPHR because of status post esophagectomy with gastric tube reconstruction and his advanced age

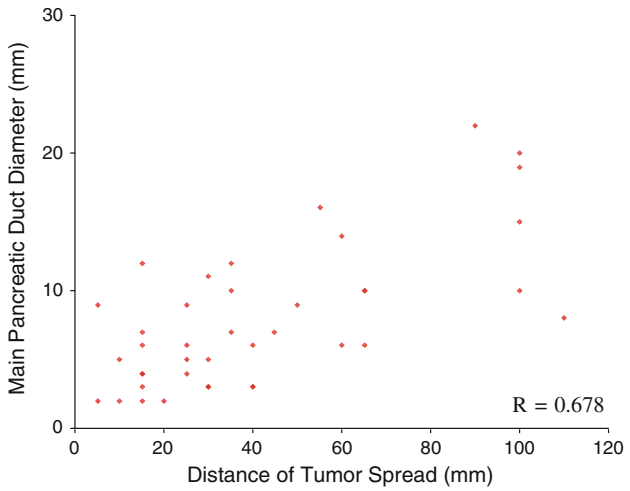

Fig. 1 The two independent data points (the maximum diameter of the main pancreatic duct and the distance of tumor spread in the main pancreatic duct of IPMN) were analyzed regarding the correlation between them. In our study, the distance of tumor spread in the main pancreatic duct of IPMN was correlated with the maximum diameter of the duct ($R = 0.678$)

invasion, indications for surgery, and, finally, the appropriate area and extent of resection. In reported series based on radiographic classification of the IPMN type, patients with suspected main duct involvement show a 35–80% incidence of invasive pancreatic cancer at the time of surgical resection [10, 15, 18]. The rate of mixed-type IPMN showing an invasive pathology at the time of resection is 23–57% [10, 15, 18–21]. Based on these data, it is useful to divide IPMNs into those that do and do not involve the main duct because a significant change in the rate of cancer is seen with main duct involvement.

Table 3 The relationship between the distance of tumor spread in the main pancreatic duct of IPMN and the maximum diameter of the main pancreatic duct (mpd)

The maximum diameter of mpd (mm)	*n*		χ^2 test *P* value
	The distance of tumor spread in the mpd of IPMN		
	≥40 mm	<40 mm	
≥6	15	9	<0.001
<6	2	14	

The resection line was determined according to the macroscopic types described above; the mean of mpd− (13.6 ± 12.4 mm) in the histopathological examination was an acceptable distance in terms of the surgical margin for IPMN because of the absence of local recurrence in the remnant pancreas in our study. In patients with suspected invasive IPMC, retroperitoneal spreading should also be taken into consideration when deciding on the surgical margin to resect the pancreas.

The positive rates of the pancreatic cut end margin of frozen sections (29.7%) and that of the final histopathological diagnosis (26.2%) were deemed appropriate because it is expected that a resection line near the tumor (greater residual pancreatic volume) results in a higher positive rate, and a resection line far from the tumor (lesser residual pancreatic volume) leads to a lower positive rate. With additional resection based on the frozen sections below this positive rate, we would be able to reduce any unnecessary loss of endocrine/exocrine function of the pancreas. Achieving a margin of 2 cm might be difficult in some cases due to the residual pancreatic volume or anatomical factors. In those cases, total pancreatectomy may be avoided in some, taking the patient's overall health status or available support into consideration in cases positive for adenoma. However, some patients may require total pancreatectomy to achieve complete resection in cases of CIS; the indication for this, however, must be examined very carefully because total pancreatectomy causes severe and permanent endocrine/exocrine pancreatic insufficiency. Because most IPMNs are slow-growing, affect elderly people, and the prognosis may be favorable even when the IPMN is malignant, the benefits of such an aggressive treatment must be balanced against operative and postoperative risks [8, 22].

Preoperative, adequate, reliable examination is essential to shorten the time and improve the quality of surgery, and it is important for surgeons to make a definitive decision preoperatively. Several studies have demonstrated that imaging procedures, including CT, EUS, ERCP, or MRCP,

are unreliable for predicting the extent of IPMN lesions [3, 8, 23]. Full visualization of the ductal system and either the main duct- or branch duct-type IPMN by ERCP is frequently difficult due to the presence of viscid mucin. The maximum diameter of the main pancreatic duct is measurable in millimeters by AUS or EUS. The diameter of the main pancreatic duct is generally larger in malignant than in benign cases of IPMN [11]. Our study suggested that it could also be a predictor of DTS in the main pancreatic duct of IPMN. In particular, cases showing strong dilatation of the main pancreatic duct (maximum diameter $\geq$6 mm) revealed a significantly greater spreading distance (mpd+ $\geq$40 mm).

To evaluate the modality for the examination of the pancreatic duct, the indication for POPS is limited to cases with a wide-open orifice of the ampulla of Vater, and the incidence of complications, especially pancreatitis, is not low. Recently, we recommended IDUS for the evaluation of IPMN distribution in pre/postoperative discussions with endoscopists because of the ability to observe the intraductal lesions and peripancreatic anatomy simultaneously to guide the resection line. In fact, IDUS provided concrete information on the resection line and its distance from the portal vein in our study. It was a useful modality to decide on the position of the resection line in the surgical field.

In conclusion, DTS offered us important insights about the position for resecting the pancreas and the positive rate at the cut end margin in IPMN in our study. Furthermore, the maximum diameter of the main pancreatic duct may be a predictor of DTS.

References

1. Paye F, Sauvanet A, Terris B, Ponsot P, Vilgrain V, Hammel P, et al. Intraductal papillary mucinous tumors of the pancreas: pancreatic resections guided by preoperative morphological assessment and intraoperative frozen section examination. Surgery. 2000;127:536–44.
2. Gigot JF, Deprez P, Sempoux C, Descamps C, Metairie S, Glineur D, 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;136:1256–62.
3. Couvelard A, Sauvanet A, Kianmanesh R, Hammel P, Colnot N, Lévy P, 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;242:774–8.
4. Sauvanet A, Partensky C, Sastre B, Gigot JF, Fagniez PL, Tuech JJ, et al. Medial pancreatectomy: a multi-institutional retrospective study of 53 patients by the French Pancreas Club. Surgery. 2002;132:836–43.
5. Schnelldorfer T, Sarr MG, Nagorney DM, Zhang L, Smyrk TC, Qin R, et al. Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. Arch Surg. 2008;143:639–46.
6. King J, Kazanjian K, Matsumoto J, Reber HA, Yeh MW, Hines OJ, et al. Distal pancreatectomy: incidence of postoperative diabetes. J Gastrointest Surg. 2008;12:1548–53.
7. Nagai K, Doi R, Kida A, Kami K, Kawaguchi Y, Ito T, et al. Intraductal papillary mucinous neoplasms of the pancreas: clinicopathologic characteristics and long-term follow-up after resection. World J Surg. 2008;32:271–8.
8. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. Pancreas. 2004;28:282–8.
9. Terris B, Ponsot P, Paye F, Hammel P, Sauvanet A, Molas G, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. Am J Surg Pathol. 2000;24:1372–7.
10. Salvia R, Fernández-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg. 2004;239:678–85.
11. Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann Surg. 1998;228:685–91.
12. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2004;28:977–87.
13. Adsay NV, Merati K, Basturk O, Iacobuzio-Donahue C, Levi E, Cheng JD, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol. 2004;28:839–48.
14. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International Association of Pancreatology: international consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17–32.
15. Waters JA, Schmidt CM. Intraductal papillary mucinous neoplasm—when to resect? Adv Surg. 2008;42:87–108.
16. Farnell MB. Surgical management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. J Gastrointest Surg. 2008;12:414–6.
17. Sugiyama M, Suzuki Y, Abe N, Mori T, Atomi Y. Management of intraductal papillary mucinous neoplasm of the pancreas. J Gastroenterol. 2008;43:181–5.
18. Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007;246:644–51.
19. Yang AD, Melstrom LG, Bentrem DJ, Ujiki MB, Wayne JD, Strouch M, et al. Outcomes after pancreatectomy for intraductal papillary mucinous neoplasms of the pancreas: an institutional experience. Surgery. 2007;142:529–34.
20. Ishida M, Egawa S, Aoki T, Sakata N, Mikami Y, Motoi F, et al. Characteristic clinicopathological features of the types of intraductal papillary-mucinous neoplasms of the pancreas. Pancreas. 2007;35:348–52.
21. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg. 2004;239:788–97.

22. Kim SC, Park KT, Lee YJ, Lee SS, Seo DW, Lee SK, et al. Intraductal papillary mucinous neoplasm of the pancreas: clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. J Hepatobiliary Pancreat Surg. 2008;15:183–8.

23. Waters JA, Schmidt CM, Pinchot JW, White PB, Cummings OW, Pitt HA, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg. 2008;12:101–9.