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Review Article

Malignant Potential of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Abstract
An intraductal papillary mucinous neoplasm (IPMN) is now a well-recognized disease entity. In general, the prognosis of IPMN is much more favorable than that of pancreatic ductal adenocarcinoma (PDAC). However, IPMN has a broad biological spectrum and it sometimes progresses, slowly showing neoplastic transformations. International consensus guidelines have been recently proposed for the management of IPMN. While they significantly contribute to appropriate management of IPMN, various issues including the natural history and malignant potential of IPMN are not fully elucidated. This review focuses on the malignant potential, including the postoperative recurrence of IPMN, coincidence of IPMN with PDAC, and extrapancreatic malignancy that may affect the long-term survival of the patients rather than IPMN itself.

Key words Intraductal papillary mucinous neoplasm · Pancreatic ductal adenocarcinoma · Extrapancreatic malignancy · Recurrence

Introduction

Noninflammatory cystic lesions of the pancreas are now frequently encountered due to recent improvements in imaging technology. The World Health Organization (WHO) classified the cystic mucin-producing neoplasms into two separate entities, intraductal papillary mucinous tumors and mucinous cystic tumors, in 1996.[1] More recently, the two tumors were defined as an intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN).[2] Intraductal papillary mucinous neoplasm is a widely recognized distinct entity characterized by papillary proliferations of mucin-producing epithelial cells with excessive mucus production and cystic dilatation of the pancreatic ducts.[3–7] An IPMN has malignant potential and encompasses a broad histological spectrum ranging from adenomas to invasive carcinomas.[3–7] Furthermore it progresses slowly, thus showing a spectrum of neoplastic transformations, and it is also characterized by a more favorable prognosis than pancreatic ductal adenocarcinoma (PDAC).[8–11] The international consensus guidelines for the management of IPMN were proposed in 2006 by the International Association of Pancreatology.[4] Although the guidelines greatly contribute to appropriate clinical management of IPMN, further studies are clearly required to enhance the understanding of this unique disease entity.

While there have been advances in the understanding of predictors for malignancy before surgery and prognostic factors, various issues including the natural history and malignant potential of IPMN have not been fully elucidated. Recently, IPMN has been receiving more attention because of a relationships with PDAC.[12–15] Another unique characteristic of IPMN is the high incidence of extrapancreatic malignancy (EPM). This review focuses on the malignant potential including postoperative recurrence of IPMN, coincidence of IPMN with PDAC, and EPM that may affect the long-term survival of patients rather than IPMN itself. Appropriate standard algorithms for either surgical management or conservative therapy should therefore be established in the future, based on the malignant potentials of IPMN.

Classification of IPMN

According to the WHO classification, IPMN is defined as an intraductal mucin-producing neoplasm of the main pancreatic duct or side branches, with variable degrees of papillary formation, mucin production, and

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cystic dilation.[1,2] Intraductal papillary mucinous neoplasm can be classified as a main duct type, branch duct type, or combined type, based on the imaging characteristics and histological examination.[4] Intraductal papillary mucinous neoplasms represent intraductal components with various degrees of cytoarchitectural atypia from adenoma (low-grade dysplasia), through borderline (moderate dysplasia) to carcinoma in situ (CIS; high-grade dysplasia) and invasive carcinoma.[1,2] There have been a considerable number of studies evaluating prevalence of malignancy of IPMN subtypes. These studies generally found that the incidence of malignancy, including CIS and invasive carcinoma, in patients with main duct IPMN (57%–92%) was significantly higher than in those with branch duct IPMN (6%–46%).[14–22] Some authors noted the prevalence of only invasive carcinoma at diagnosis to be high in main duct IPMN (23%–57%) and lower in branch duct IPMN (0%–31%). Branch duct IPMNs have been reported to present with lower frequency of aggressive histological features and a better prognosis in comparison to main duct IPMN.[14–22] Therefore, the classification between the two types, namely main duct and branch duct types, is considered to have prognostic implications. More recently, IPMNs have been proposed to be classified into four distinct types, namely gastric, intestinal, pancreatobiliary, and oncocytic type, based on the morphological characteristics and immunohistochemical features of mucin glycoproteins such as MUC1, MUC2, and MUC5AC.[23–27] The intestinal type (MUC1-negative and MUC2- and MUC5AC-positive) frequently shows moderate to severe dysplasia. The pancreatobiliary type (MUC2-negative, and MUC1- and MUC5AC-positive) shows severe atypia corresponding to CIS. The gastric type (MUC1- and MUC2-negative and MUC5AC-positive) is rarely associated with invasive carcinomas and often seen in branch duct IPMN.[23–27] Patients with the intestinal type had poorer survival than those with the gastric type. The 5-year relative survival rates were 62.3% for the intestinal type and 100% for the gastric type.[25] Large-scale studies may therefore be required to define the significance of the mucin profiles in IPMNs.

Natural History of IPMNs

Recent prospective studies have described the natural history of IPMNs as evaluated by computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and endoscopic ultrasonography (EUS).[28–35] Tanno et al.[32] evaluated the long-term follow-up results of 82 asymptomatic branch duct IPMNs without mural nodules. They reported that only 9/82 (11%) of IPMNs exhibited an increase in cyst size (>10 mm) and 4/82 (4.9%) developed mural nodules, but none of these IPMNs developed invasive carcinomas. Recent prospective studies by Pelaez-Luna et al.[33,34] revealed that malignancy was present in 9/61 (15%) of branch duct IPMNs with at least one of the consensus indications for resection (CIR; i.e., cyst-related symptoms, cyst size >30 mm, main pancreatic duct >10 mm, mural nodules, and positive cytology) and 0/16 of IPMNs without CIR, although their specificity was low. Rautou et al.[35] have reported that the only factor associated with the signs suggesting malignant transformation was an increase in cyst size to more than 5 mm during the follow-up of branch duct IPMNs.

There is a widely recognized consensus that all main duct IPMNs and symptomatic branch duct IPMNs should be surgically resected. Recent prospective studies of the natural history of IPMNs show that branch duct IPMNs with main duct dilatation, or a mural nodule, or of cyst size >30 mm should be indications for resection, whereas asymptomatic branch duct IPMN <30 mm without main duct dilatation and without a mural nodule can be followed using periodic imaging tests.[28–35] The recommendation by the international consensus guidelines in 2006[4] has been validated in the latest prospective studies and some large retrospective studies.[36,37] However, a prospective analysis by Walsh et al.[38] revealed that cyst size alone is not a reasonable risk factor for malignancy. Nagai et al.[39,40] reported that even patients with cystic lesions <30 mm and no mural nodules had malignant IPMNs (CIS and invasive carcinoma), although a multivariate analysis showed the cyst size to be the only independent predictor of malignancy. Further prospective analyses of the natural history of IPMNs are therefore expected to clarify the risk for malignant transformation during the follow-up and to establish a strategy for the conservative management of branch duct IPMNs.

Invasive Carcinomas Derived from IPMN

The Japan Pancreas Society (JPS) defined a noninvasive type of IPMN as limited to the pancreatic duct and a minimally invasive type as having invaded slightly to the pancreatic parenchyma beyond the pancreatic duct wall.[4,41] On the other hand, invasive carcinoma derived from IPMN is definitely classified under "invasive carcinoma originating in an intraductal tumor" as a subtype of invasive ductal carcinomas, i.e., conventional PDAC.[41] Invasive carcinoma derived from IPMN is characteristic of macroscopic invasion showing either gross or histological evidence of a pre-existing IPMN.[41] However, the terminology remains confusing in regard of the fact that "invasive IPMN" is likely to mean both minimally invasive IPMN and invasive carcinomas derived from IPMN, since the depth of invasion has not yet been clearly

defined. In fact, while the 5-year survival rate of noninvasive IPMN is 85%–100%, that for invasive IPMN ranges from 25% to 65%.[21,22,42–46] A multivariate analysis further indicated the invasive growth of IPMN to be the only independent prognostic factor.[42] Therefore, it is critical to establish a clear definition to distinguish between minimally invasive IPMN and invasive carcinomas derived from IPMN for an accurate analysis to reveal the whole natural history of IPMN.

Nevertheless, even invasive carcinoma derived from IPMN has a more favorable prognosis in comparison to conventional PDAC not arising in the setting of IPMN.[47–49] One of the main reasons for a better postoperative survival in patients with invasive carcinoma derived from IPMN might be due to the early detection and diagnosis, thus enabling a resection at an earlier stage in comparison to conventional PDAC. In addition, the less frequent detection of the pathological factors associated with tumor invasiveness of the invasive component of IPMN might suggest a less aggressive biological behavior that may contribute to a slowly progressive nature and a favorable surgical outcome in comparison to conventional PDAC.

Several studies have reported that patients with noninvasive IPMN are on average 5–7 years younger than patients who have IPMN with associated invasive carcinomas, thus suggesting a time lag of 5–7 years from the progression of adenoma to invasive carcinoma.[8,21,22] Recently, molecular biological analyses have identified accumulations of some genetic alterations from noninvasive IPMN to invasive carcinoma derived from IPMN.[50–53] A recent study by Fritz et al.[52] revealed that IPMNs show an accumulation of chromosomal alterations reflecting the progression from low-grade dysplasia to invasive carcinoma. Nakata et al.[53] reported that REG4 expression shows a significant increasing trend from adenoma to carcinoma, thus suggesting that REG4 might be involved in the carcinogenesis of IPMN. Further genetic analyses could therefore help to clarify the molecular mechanisms underlying the biological and clinical behavior, and the development of malignant transformation of IPMNs.

Multifocal Characteristics and Recurrence of IPMN

Mucinous cystic neoplasms are generally solitary and do not recur after a complete resection.[54] By contrast, IPMN is often multifocal. In particular, branch duct IPMN can often be multifocal and located in distant regions of the pancreas in up to 30% of patients.[55,56] However, there was no significant difference in the prevalence of malignancy between single and multifocal branch duct IPMN (13% vs 11%).[33] The CIS and invasive carcinoma of IPMN, which may be multifocal and macroscopically invisible, can also be identified by thorough examinations of all the sectioned specimens of the entire resected pancreas. Postoperative recurrence might occur in the remnant pancreas during follow-up and the recurrent tumor can be cured by a reoperation, i.e., a total pancreatectomy in most cases.[57] Several subsequent studies from other institutes have reported similar experiences. Both benign and malignant recurrence in the remnant pancreas in patients with both invasive and noninvasive IPMN is well documented.[21,22] A summary of reports describing the incident rate and pattern of recurrence after resection of IPMN is shown in Table 1.[14,16,21,22,42–45,48,57–74] The overall recurrence rate for IPMN varies from 4% to 43%. The median disease-free interval after surgery ranges from 8 to 42 months. The pattern of recurrence consists of not only local recurrence in the pancreatic bed or remnant but also distant metastases. Chari et al.[45] reported that the recurrences after the resection of invasive IPMN frequently occur at distant sites. However, the relationship between the site of recurrence and pathological findings of primary tumor remains unclear because most studies include a relatively small number of patients. Several studies have demonstrated that recurrence occurred more frequently in patients with invasive IPMN than in patients with noninvasive IPMN. To date, there is no evidence to define the frequency and type of surveillance to detect these recurrences. However, since patients with invasive IPMN are likely to have a significant risk of recurrence, they probably should be followed up every 6 months using either CT or MRI.[4] The diagnosis of postoperative recurrence is important for improving prognosis since a reoperation for recurrent IPMN can provide a complete cure. Furthermore, careful follow-up to determine the timing for reoperation could therefore be crucial, since there is no evidence on the effect of other therapeutic modalities including chemotherapy and radiation for IPMN. On the other hand, recent chemotherapeutic regimens for PDAC have significantly improved the survival of patients with PDAC. Therefore, its effect for invasive or recurrent IPMN should be evaluated in the future. In addition, another major issue in future studies may be to find molecular-biological markers to predict the risk of the multifocal characteristics and recurrence of IPMN.

Occurrence of Pancreatic Ductal Adenocarcinoma

Several reports have shown that some IPMN are accompanied by independent ordinary type PDAC (Table 2).[75–78] The synchronous and/or metachronous occurrence of PDAC concomitant with IPMN ranges from 2.5% to 9.2%. Yamaguchi et al.[75] reported that all the

Table 1. Incidence of recurrence after resection of intraductal papillary mucinous neoplasm (IPMN) in large series published between 1998 and 2008

First author[Ref.]	Year	Incidence of recurrence			Site of recurrence		Median follow-up (months)	Median disease-free interval (months)
		Total no. of IPMN patients (%)	Primary tumor					
			NI	I	Local	Distant		
Traverso[58]	1998	6/33 (19%)	0/20	6/13	NM	NM	37	13[a]
Sho[57]	1998	6/14 (43%)	4/10	2/4	6	2	38.5	38 (18–63)
Kobari[14]	1999	6/30 (20%)	NM/26	NM/4	4	2	37	NM
Yamaguchi[59]	2000	2/48 (4%)	0/33	2/15	NM	NM	NM	NM
Paye[60]	2000	10/41 (24%)	0/31	10/10	3	7	NM	NM
Cuillerier[61]	2000	15/43 (33%)	2/26	13/19	8	7	65[a]	NM
Zamora[62]	2001	3/19 (16%)	1/14	2/5	2	3	41	14 (7–27)
Falconi[44]	2001	4/51 (8%)	0/32	4/19	4	0	15[a]	42 (37–62)
Adsay[63]	2002	5/28 (18%)	2/13	3/15	1	1	35	NM
Chari[45]	2002	31/113 (27%)	5/73	26/40	12	18	40	18[a]
Nakagohri[64]	2002	3/21 (14%)	1/16	2/5	1	2	78	NM
Doi[16]	2002	3/38 (8%)	NM/16	NM/22	1	2	42[a]	22 (17–32)
Maire[48]	2002	28/73 (38%)	0/22	28/51	16	28	25	12 (0–56)
Sugiura[65]	2002	2/30 (7%)	0/27	2/3	0	2	60[a]	(16, 17)
Tollefson[66]	2003	7/21 (33%)	2/10	5/11	NM	NM	NM	NM
D'Angelica[67]	2004	12/62 (19%)	3/32	9/30	5	7	32	20 (8–70)
Salvia[22]	2004	8/137 (9%)	1/80	7/57	8	5	31	NM
Sohn[21]	2004	28/131 (20%)	7/81	21/50	NM	NM	24[a]	NM
Lee[68]	2005	6/67 (9%)	6/47	0/9	2	4	24	18 (6–31)
Wada[69]	2005	13/100 (13%)	1/75	12/25	NM	NM	56[a]	26[a]
Raut[43]	2006	7/34 (21%)	0/22	7/12	1	7	34	8 (4–25)
Takahashi[70]	2006	2/20 (10%)	1/17	1/3	0	2	64.7	(17, 25)
Yokoyama[71]	2007	5/100 (5%)	2/85	3/15	5	0	30	30 (13–73)
White[72]	2007	6/78 (8%)	6/78	0/0	6	0	40	22 (8–62)
Woo[73]	2008	3/19 (16%)	0/0	3/19	2	2	18.4	NM
Schnelldorfer[74]	2008	44/200 (22%)	11/143	33/57	18	27	NM	NM
Niedergethmann[42]	2008	23/97 (24%)	4/29	19/68	3	20	36	NM

NI, noninvasive (including adenoma, borderline, carcinoma in situ); I, invasive (including minimally invasive IPMN); NM, not mentioned
[a] Mean

Table 2. Occurrence of pancreatic ductal adenocarcinoma (PDAC) concomitant with IPMN

First author[Ref.]	Year	Occurrence of PDAC/ Total no. of IPMN patients (%)	IPMN		PDAC		
			Pathology NI/I	Location head/body/tail	Period Syn/Met	Stage[a] I/II/III/IV	Tumor resectability
Yamaguchi[75]	2002	7/76 (9.2%)	7/0	3/2/2	5/2	3/0/3/1	7/7
Kamisawa[76]	2005	3/79 (3.8%)	NM	3/0/0	2/1	0/1/1/1	2/3
Tada[77]	2006	2/80 (2.5%)	NM	1/1/0	0/2	1/0/0/1	1/2
Uehara[78]	2008	5/60[b] (8.3%)	5/0	3/1/1	0/5	0/0/3/2	4/5

Syn, synchronous; Met, metachronous; NI, noninvasive (including adenoma, borderline, carcinoma in situ); I, invasive (including minimally invasive IPMN); NM, not mentioned
[a] Classification of pancreatic carcinoma from Japan Pancreas Society[33]
[b] In this report, PDACs during follow-up of nonsurgical branch duct IPMNs were investigated

IPMNs associated with PDAC are of the branch duct type of adenoma with mild dysplasia. In their report, PDACs concomitant with IPMN were significantly smaller in diameter and earlier in tumor stage, and the survival of those patients was more favorable in comparison to the patients with sporadic PDAC alone.[75] These results suggest that the close surveillance of the pancreas in patients with IPMN may lead to the diagnosis of PDAC at an earlier stage than usual. Uehara et al.[78] reported that PDAC distinct from IPMN occurs in 5 of 60 patients (8.3%) during the follow-up of nonsurgical branch duct IPMN. The incidence of PDAC in the pancreas harboring IPMN is 1.1% per year, while that of sporadic PDAC in the control group matched for age and gender was calculated to be 0.045% per year.[78] The high prevalence of PDAC in patients with IPMN sug-

Table 3. Incidence of extrapancreatic malignancy (EPM) associated with IPMN in large series published between 1999 and 2008

First author[Ref.]	Year	No. of IPMN patients	Incidence of EPM	Common sites of EPM	Comparison[a]
Sugiyama[87]	1999	42	32%	Colon (33%), stomach (27%)	PDAC (11%)
Yamaguch[59]	2000	48	27%	Stomach (38%), colon (15%), liver (15%)	MCN (5%)
Kamisawa[76]	2005	79	35%	Stomach (30%), colon (18%), lung (10%)	—
Choi[88]	2006	61	30%	Stomach (44%), colon (22%), BD (11%)	MCN (8%), PDAC (10%)
Eguchi[89]	2006	69	38%	Colon (25%), lung (16%), stomach (13%)	PDAC (12%)
Riall[90]	2007	992	10.1%	Colon (25%), breast (18%), prostate (14%)	PDAC (10.3%)
Yoon[91]	2008	210	33.8%	Stomach (38%), colon (21%), BD (9%)	Non-IPMN PCN (12.0%)
Ishida[92]	2008	61	24.6%	Stomach (35%), colon (29%)	IPMA (16.4%) vs IPMC (8.2%)
Baumgaertner[93]	2008	178	16.8%	Breast (30%), prostate (10%), colon (10%)	Age- and gender-matched control (8.4%)

PDAC, pancreatic ductal adenocarcinoma; MCN, mucinous cystic neoplasm; Non-IPMN PCN, pancreatic cystic neoplasm excluding IPMN; BD, bile duct; IPMA, intraductal papillary mucinous adenocarcinoma; IPMC, intraductal papillary mucinous carcinoma

[a] Incidence of EPM associated with IPMN was compared to that with other pancreatic diseases

gests that IPMN may be a risk factor for development of PDAC, and that entire ductal system including the neoplastic epithelium of the pancreas with IPMN is in the premalignant state. Although relatively few studies have so far described the potential risk for the occurrence of PDAC concomitant with branch duct IPMN, the risk for coincidence of PDAC with main duct IPMN remains unclear at present.

The mechanism of development of PDAC in the pancreas harboring IPMN has not been clarified. A K-ras gene mutation, which is frequently detected in PDAC,[79,80] was also identified in IPMN.[81–83] The frequency of this mutation in IPMN increases with increasing grades of dysplasia,[84,85] suggesting that some IPMN may progress to PDAC through stepwise accumulation of genetic alterations. However, recent studies on cytogenetic alterations have reported that IPMNs have a different genetic background in comparison to conventional PDAC,[52,53] which might explain the distinctly less aggressive clinical behavior of IPMN. Takahashi et al.[86] reported that the Dpc4 tumor suppressor gene was expressed in some PDACs similar to invasive carcinoma derived from IPMN, while its expression is usually diminished in other types of PDACs, thus suggesting that two different pathways exist for pancreatic carcinogenesis. Therefore, some type of IPMN may be a precursor to PDAC, although further epidemiological, clinicopathological, and genetic studies are needed to clarify the mechanism of pancreatic carcinogenesis.

Since the prognosis of IPMN is much more favorable in comparison to that of conventional PDAC,[47–49] a close surveillance may be critical to detect the PDAC that may develop during the follow-up of IPMN. An appropriate follow-up strategy for conservative management in both postsurgical and nonsurgical cases should be established in the near future based on the malignant potential of IPMN.

Incidence of Extrapancreatic Malignancy Associated with IPMN

Several studies have recently described an increased risk of associated EPM in patients with IPMN (Table 3).[59,76,87–93] Most studies have been conducted in Asia including Japan and Korea, and there are a few clinical studies on EPM from Europe and the United States. The incidence of EPM ranges from 10.1% to 38% of IPMN. Some have also shown that it is higher in comparison to MCN or PDAC. However, the potential biases may include the shorter postoperative follow-up period in patients with PDAC due to their poor surgical outcome, and the younger age for MCN patients in comparison to IPMN patients. In addition, most authors reported that the digestive system is the most common

Table 4. Current issues regarding malignant potential of IPMN

- To establish follow-up strategy for conservative management of IPMN (branch duct IPMN)
- To establish surveillance strategy after curative resection of IPMN
- To define a clear criteria for invasive IPMN
- To evaluate the effect of chemotherapy or radiation on invasive IPMN
- To discover a molecular-biological marker to predict the malignancy and multifocality of IPMN

site of EPM.[87–92] Riall et al.[90] reported a population-based analysis that revealed the incidence of EPM in patients with invasive IPMN (10.1%) was similar to that of patients with sporadic PDAC (10.3%). Baumgaertner et al.[93] reported the first case–control study concerning a large series of 178 patients with histologically proven IPMN in comparison to 356 age- and gender-matched controls. Their results demonstrated a significantly higher prevalence of EPM in IPMN patients (16.8%) than that in control (8.4%).[93] However, the type of EPM is not different between IPMN and control groups, and the most common site of EPM in patients with IPMN and controls were the breast, prostate, and colon/rectum.[93] No definitive conclusion on the precise risk of EPM can be made because of the limited number of cases and short follow-up in relatively few clinical studies. However, considerable attention may be required in patients with IPMN for the possible occurrence of EPM that can determine the long-term survival of these patients.

Conclusion

Intraductal papillary mucinous neoplasm has recently been noted to have various malignant potentials, not only in malignancy derived from IPMN but also in the recurrence and occurrence of PDAC and EPM that can affect the long-term survival of patients rather than IPMN itself. An appropriate standard algorithm for conservative therapy or the postsurgical management of IPMN should be established in future, based on the unique malignant potential of IPMN. Furthermore, nationwide registration may be required to clarify several current issues regarding the malignant potential and management of IPMN (Table 4). IPMN will not only offer an attractive model for investigating the mechanism of pancreatic carcinogenesis, but may also allow for the development of new treatment strategies for PDAC.

References

1. Klöppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. World Health Organization international histological classification of tumors. Histological typing of tumors of the exocrine pancreas. 2nd ed. Berlin: Springer; 1996. p. 1–61.
2. Longnecker DS, Adler G, Hruban RH, Klöppel G. Intraductal papillary-mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumors. Pathology and genetics of tumors of the digestive system. Lyon: IARC Press; 2000. p. 237–41.
3. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. Pancreas 2004;28:282–8.
4. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.
5. Ohashi K, Murakami Y, Maruyama M, Takekoshi T, Ota H, Ohashi I, et al. Four cases of "mucin-producing" cancer of the pancreas on specific findings of the papilla of Vater. Prog Dig Endosc 1982;20:348–51.
6. Solcia E, Capella C, Klöppel G. Tumors of the pancreas. In: Rosai J, Sobin LH, editors. Atlas of tumor pathology. Fascicle 20, 3rd ed. Washington DC: Armed Forces Institute of Pathology; 1997. p. 1–262.
7. Egawa S, Takeda K, Fukuyama S, Motoi F, Sunamura M, Matsuno S. Clinicopathological aspects of small pancreatic cancer. Pancreas 2004;28:235–40.
8. Obara T, Maguchi H, Saitoh Y, Itoh A, Arisato S, Ashida T, et al. Mucin-producing tumor of the pancreas: natural history and serial pancreatogram changes. Am J Gastroenterol 1993;88:564–9.
9. Lévy P, Jouannaud V, O'Toole D, Couvelard A, Vullierme MP, Palazzo L, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. Clin Gastroenterol Hepatol 2006;4:460–8.
10. Sugiyama M, Atomi Y, Kuroda A. Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. Surgery 1997;122:617–25.
11. Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann Surg 1998;228:685–91.
12. Takaori K, Kobashi Y, Matsusue S, Matsui K, Yamamoto T. Clinicopathological features of pancreatic intraepithelial neoplasias and their relationship to intraductal papillary mucinous tumors. J Hepatobiliary Pancreat Surg 2003;10:125–36.
13. Kitago M, Ueda M, Aiura K, Suzuki K, Hoshimoto S, Takahashi S, et al. Comparison of K-ras point mutation distributions in intraductal papillary-mucinous tumors and ductal adenocarcinoma of the pancreas. Int J Cancer 2004;110:177–82.
14. Kobari M, Egawa S, Shibuya K, Shimamura H, Sunamura M, Takeda K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. Arch Surg 1999;134:1131–6.
15. 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.
16. Doi R, Fujimoto K, Wada M, Imamura M. Surgical management of intraductal papillary mucinous tumor of the pancreas. Surgery 2002;132: 80–5.
17. Matsumoto T, Aramaki M, Yada K, Hirano S, Himeno Y, Shibata K, et al. Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. J Clin Gastroenterol 2003;36:261–5.

18. Choi BS, Kim TK, Kim AY, Kim KW, Park SW, Kim PN, et al. Differential diagnosis of benign and malignant intraductal papillary mucinous tumors of the pancreas: MR cholangio-pancreatography and MR angiography. Korean J Radiol 2003;4:157–62.
19. Kitagawa Y, Unger TA, Taylor S, Kozarek RA, Traverso LW. Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. J Gastrointest Surg 2003;7: 12–9.
20. Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumors of the pancreas. Br J Surg 2003;90:1244–9.
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;239:788–99.
22. Salvia R, Fernandez-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 longterm survival following resection. Ann Surg 2004;239: 678–87.
23. Lüttges J, Zamboni G, Longnecker D, Klöppel G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. Am J Surg Pathol 2001;25:942–8.
24. Furukawa T, Klöppel G, Volkan AN, Albores-Saavedra J, Fukushima N, Horii A, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Arch 2005;447:794–9.
25. 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.
26. Hruban RH, Takaori K, Canto M, Fishman EK, Campbell K, Brune K, et al. Clinical importance of precursor lesions in the pancreas. J Hepatobiliary Pancreat Surg 2007;14:255–63.
27. Katabi N, Klimstra DS. Intraductal papillary mucinous neoplasms of the pancreas: clinical and pathological features and diagnostic approach. J Clin Pathol 2008;61:1303–13.
28. Yamada Y, Mori H, Matsumoto S, Kamei N, Hongo N. Invasive carcinomas derived from intraductal papillary mucinous neoplasms of the pancreas: a long-term follow-up assessment with CT imaging. J Comput Assist Tomogr 2006;30(6):885–90.
29. Guarise A, Faccioli N, Ferrari M, Salvia R, Mucelli RP, Morana G, et al. Evaluation of serial changes of pancreatic branch duct intraductal papillary mucinous neoplasms by follow-up with magnetic resonance imaging. Cancer Imaging 2008;8:220–8.
30. Yamaguchi T, Baba T, Ishihara T, Kobayashi A, Nakamura K, Tadenuma H, et al. Long-term follow-up of intraductal papillary mucinous neoplasm of the pancreas with ultrasonography. Clin Gastroenterol Hepatol 2005;3(11):1136–43.
31. Kobayashi G, Fujita N, Noda Y, Ito K, Horaguchi J, Takasawa O, et al. Mode of progression of intraductal papillary-mucinous tumor of the pancreas: analysis of patients with follow-up by EUS. J Gastroenterol 2005;40(7):744–51.
32. Tanno S, Nakano Y, Nishikawa T, Nakamura K, Sasajima J, Minoguchi M, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut 2007;57:339–43.
33. Pelaez-Luna M, Chari ST, Smyrk TC, Takahashi N, Clain JE, Levy MJ, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. Am J Gastroenterol 2007;102:1759–64.
34. Gill KR, Pelaez-Luna M, Keaveny A, Woodward TA, Wallace MB, Chari ST, et al. Branch duct intraductal papillary mucinous neoplasm of the pancreas in solid organ transplant recipients. Am J Gastroenterol 2009;104:1256–61.
35. Rautou PE, Lévy P, Vullierme MP, O'Toole D, Couvelard A, Cazals-Hatem D, et al. Morphologic changes in branch duct intraductal papillary mucinous neoplasms of the pancreas: a midterm follow-up study. Clin Gastroenterol Hepatol 2008;6:807–14.
36. Lee CJ, Scheiman J, Anderson MA, Hines OJ, Reber HA, Farrell J, et al. Risk of malignancy in resected cystic tumors of the pancreas </=3 cm in size: is it safe to observe asymptomatic patients? A multiinstitutional report. J Gastrointest Surg 2008;12:234–42.
37. Rodriguez JR, Salvia R, Crippa S, Warshaw AL, Bassi C, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology 2007;133:72–9.
38. Walsh RM, Vogt DP, Henderson JM, Hirose K, Mason T, Bencsath K, et al. Management of suspected pancreatic cystic neoplasms based on cyst size. Surgery 2008;144:677–84.
39. Nagai K, Doi R, Ito T, Kida A, Koizumi M, Masui T, et al. Single-institution validation of the international consensus guidelines for treatment of branch duct intraductal papillary mucinous neoplasms of the pancreas. J Hepatobiliary Pancreat Surg 2009;16: 353–8.
40. 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.
41. Japan Pancreas Society. Classification of pancreatic carcinoma. 2nd ed, revised in English. Tokyo: Kanehara; 2003.
42. Niedergethmann M, Grutzmann R, Hildenbrand R, Dittert D, Aramin N, Franz M, et al. Outcome of invasive and noninvasive intraductal papillary-mucinous neoplasms of the pancreas (IPMN): A 10-year experience. World J Surg 2008;32:2253–60.
43. Raut CP, Cleary KR, Staerkel GA, Abbruzzese JL, Wolff RA, Lee JH, et al. Intraductal papillary mucinous neoplasms of the pancreas: effect of invasion and pancreatic margin status on recurrence and survival. Ann Surg Oncol 2006;13:582–94.
44. Falconi M, Salvia R, Bassi C, Zamboni G, Talamini G, Pederzoli P. Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas. Br J Surg 2001;88: 376–81.
45. Chari ST, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Raimondo M, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 2002;123:1500–7.
46. Serikawa M, Sasaki T, Fujimoto Y, Kuwahara K, Chayama K. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol 2006;40:856–62.
47. Shimada K, Sakamoto Y, Sano T, Kosuge T, Hiraoka N. Invasive carcinomas originating in intraductal papillary mucinous neoplasm of the pancreas: a clinicopathologic comparison with a common type of invasive ductal carcinoma. Pancreas 2006;32: 281–7.
48. Maire F, Hammel P, Terris B, Paye F, Scoazec JY, Cellier C, et al. Prognosis of malignant intraductal papillary mucinous tumours of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. Gut 2002;51:717–22.
49. Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, Lillemoe KD. Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. Ann Surg 2001;234:313–21.
50. Ueda M, Miura Y, Kunihiro O, Ishikawa T, Ichikawa Y, Endo I, et al. MUC1 overexpression is the most reliable marker of invasive carcinoma in intraductal papillary-mucinous tumor (IPMT). Hepatogastroenterology 2005;52:398–403.
51. Yonezawa S, Horinouchi M, Osaka M, Kubo M, Takao S, Arimura Y, et al. Gene expression of gastric type mucin in pancreatic tumors: its relation with biological behavior of the tumor. Pathol Int 1999;49:45–54.
52. Fritz S, Fernandez-del Castillo C, Mino-Kenudson M, Crippa S, Deshpande V, Lauwers GY, et al. Global genomic analysis of intraductal papillary mucinous neoplasms of the pancreas reveals

significant molecular differences compared to ductal adenocarcinoma. Ann Surg 2009;249:440–7.
53. Nakata K, Nagai E, Ohuchida K, Aishima S, Hayashi A, Miyasaka Y, et al. REG4 is associated with carcinogenesis in the "intestinal" pathway of intraductal papillary mucinous neoplasms. Mod Pathol 2009;22:460–8.
54. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol 1999;23:410–22.
55. Kaneko T, Nakao A, Inoue S, Sugimoto H, Hatsuno T, Ito A, et al. Intraoperative ultrasonography by high-resolution annular array transducer for intraductal papillary mucinous tumors of the pancreas. Surgery 2001;129:55–65.
56. Kaneko T, Nakao A, Nomoto S, Furukawa T, Hirooka Y, Nakashima N, et al. Intraoperative pancreatoscopy with the ultrathin pancreatoscope for mucin-producing tumors of the pancreas. Arch Surg 1998;133:263–7.
57. Sho M, Nakajima Y, Kanehiro H, Hisanaga M, Nishio K, Nagao M, et al. Pattern of recurrence after resection for intraductal papillary mucinous tumors of the pancreas. World J Surg 1998;22: 874–8.
58. Traverso LW, Peralta EA, Ryan JA Jr, Kozarek RA. Intraductal neoplasms of the pancreas. Am J Surg 1998;175:426–32.
59. Yamaguchi K, Yokohata K, Noshiro H, Chijiiwa K, Tanaka M. Mucinous cystic neoplasm of the pancreas or intraductal papillary-mucinous tumor of the pancreas. Eur J Surg 2000;166: 141–8.
60. 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.
61. Cuillerier E, Cellier C, Palazzo L, Devière J, Wind P, Rickaert F, et al. Outcome after surgical resection of intraductal papillary and mucinous tumors of the pancreas. Am J Gastroenterol 2000;95: 441–5.
62. Zamora C, Sahel J, Cantu DG, Heyries L, Bernard JP, Bastid C, et al. Intraductal papillary or mucinous tumors (IPMT) of the pancreas: report of a case series and review of the literature. Am J Gastroenterol 2001;96:1441–7.
63. Adsay NV, Conlon KC, Zee SY, Brennan MF, Klimstra DS. Intraductal papillary-mucinous neoplasms of the pancreas: an analysis of in situ and invasive carcinomas in 28 patients. Cancer 2002;94: 62–77.
64. Nakagohri T, Asano T, Kenmochi T, Urashima T, Ochiai T. Long-term surgical outcome of noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma of the pancreas. World J Surg 2002;26:1166–9.
65. Sugiura H, Kondo S, Islam HK, Ito K, Ono K, Morikawa T, et al. Clinicopathologic features and outcomes of intraductal papillary-mucinous tumors of the pancreas. Hepatogastroenterology 2002; 49:263–7.
66. Tollefson MK, Libsch KD, Sarr MG, Chari ST, DiMagno EP, Urrutia R, et al. Intraductal papillary mucinous neoplasm: did it exist prior to 1980? Pancreas 2003;26:e55–8.
67. 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;239:400–8.
68. Lee SY, Lee KT, Lee JK, Jeon YH, Choi D, Lim JH, et al. Long-term follow up results of intraductal papillary mucinous tumors of pancreas. J Gastroenterol Hepatol 2005;20:1379–84.
69. Wada K, Kozarek RA, Traverso LW. Outcomes following resection of invasive and noninvasive intraductal papillary mucinous neoplasms of the pancreas. Am J Surg 2005;189:632–7.
70. Takahashi H, Nakamori S, Nakahira S, Tsujie M, Takahshi Y, Marubashi S, et al. Surgical outcomes of noninvasive and minimally invasive intraductal papillary-mucinous neoplasms of the pancreas. Ann Surg Oncol 2006;13:955–60.
71. Yokoyama Y, Nagino M, Oda K, Nishio H, Ebata T, Abe T, et al. Clinicopathologic features of re-resected cases of intraductal papillary mucinous neoplasms (IPMNs). Surgery 2007;142:136–42.
72. White R, D'Angelica M, Katabi N, Tang L, Klimstra D, Fong Y, et al. Fate of the remnant pancreas after resection of noninvasive intraductal papillary mucinous neoplasm. J Am Coll Surg 2007;204:987–95.
73. Woo SM, Ryu JK, Lee SH, Yoo JW, Park JK, Kim YT, et al. Survival and prognosis of invasive intraductal papillary mucinous neoplasms of the pancreas: comparison with pancreatic ductal adenocarcinoma. Pancreas 2008;36:50–5.
74. 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.
75. Yamaguchi K, Ohuchida J, Ohtsuka T, Nakano K, Tanaka M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinomas of the pancreas. Pancreatology 2002;2: 484–90.
76. Kamisawa T, Tu Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Malignancies associated with intraductal papillary mucinous neoplasm of the pancreas. World J Gastroenterol 2005;11:5688–90.
77. Tada M, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, et al. Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. Clin Gastroenterol Hepatol 2006;4:1265–70.
78. Uehara H, Nakaizumi A, Ishikawa O, Iishi H, Tatsumi K, Takakura R, et al. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. Gut 2008;57:1561–5.
79. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 1988;53:549–54.
80. Kondo H, Sugano K, Fukayama N, Kyogoku A, Nose H, Shimada K, et al. Detection of point mutations in the K-ras oncogene at codon 12 in pure pancreatic juice for diagnosis of pancreatic carcinoma. Cancer 1994;73:1589–94.
81. Tada M, Omata M, Ohto M. Ras gene mutations in intraductal papillary neoplasms of the pancreas. Analysis in five cases. Cancer 1991;67:634–7.
82. Uehara H, Nakaizumi A, Baba M, Iishi H, Tatsuta M, Kitamura T, et al. Diagnosis of pancreatic cancer by K-ras point mutation and cytology of pancreatic juice. Am J Gastroenterol 1996;91: 1616–21.
83. Moskaluk CA, Hruban RH, Kern SE. p16 and K-ras gene mutations in the intraductal precursors of human pancreatic adenocarcinoma. Cancer Res 1997;57:2140–3.
84. Yoshizawa K, Nagai H, Sakurai S, Hironaka M, Morinaga S, Saitoh K, et al. Clonality and K-ras mutation analyses of epithelia in intraductal papillary mucinous tumor and mucinous cystic tumor of the pancreas. Virchows Arch 2002;441:437–43.
85. Z'graggen K, Rivera JA, Compton CC, Pins M, Werner J, Fernández-del Castillo C, et al. Prevalence of activating K-ras mutations in the evolutionary stages of neoplasia in intraductal papillary mucinous tumors of the pancreas. Ann Surg 1997;226: 491–8.
86. Takahashi H, Oda T, Hasebe T, Aoyagi Y, Kinoshita T, Konishi M, et al. Biologically different subgroups of invasive ductal carcinoma of the pancreas: Dpc4 status according to the ratio of intraductal carcinoma components. Clin Cancer Res 2004;10:3772–9.
87. Sugiyama M, Atomi Y. Extrapancreatic neoplasms occur with unusual frequency in patients with intraductal papillary mucinous tumors of the pancreas. Am J Gastroenterol 1999;94:470–3.
88. Choi MG, Kim SW, Han SS, Jang JY, Park YH. High incidence of extrapancreatic neoplasms in patients with intraductal papillary mucinous neoplasms. Arch Surg 2006;141:51–6.

89. Eguchi H, Ishikawa O, Ohigashi H, Tomimaru Y, Sasaki Y, Yamada T, et al. Patients with pancreatic intraductal papillary mucinous neoplasms are at high risk of colorectal cancer development. Surgery 2006;139:749–54.
90. Riall TS, Stager VM, Nealon WH, Townsend CM Jr, Kuo YF, Goodwin JS, et al. Incidence of additional primary cancers in patients with invasive intraductal papillary mucinous neoplasms and sporadic pancreatic adenocarcinomas. J Am Coll Surg 2007; 204:803–13.
91. Yoon WJ, Ryu JK, Lee JK, Woo SM, Lee SH, Park JK, et al. Extrapancreatic malignancies in patients with intraductal papillary mucinous neoplasm of the pancreas: prevalence, associated factors, and comparison with patients with other pancreatic cystic neoplasms. Ann Surg Oncol 2008;15:3193–8.
92. Ishida M, Egawa S, Kawaguchi K, Aoki T, Sakata N, Mikami Y, et al. Synchronous and metachronous extrapancreatic malignant neoplasms in patients with intraductal papillary-mucinous neoplasm of the pancreas. Pancreatology 2008;8:577–82.
93. Baumgaertner I, Corcos O, Couvelard A, Sauvanet A, Rebours V, Vullierme M-P, et al. Prevalence of extrapancreatic cancers in patients with histologically proven intraductal papillary mucinous neoplasms of the pancreas: a case-control study. Am J Gastroenterol 2008;103:2878–82.