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Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

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ABSTRACT

The international consensus guidelines for management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasm of the pancreas established in 2006 have increased awareness and improved the management of these entities. During the subsequent 5 years, a considerable amount of information has been added to the literature. Based on a consensus symposium held during the 14th meeting of the International Association of Pancreatology in Fukuoka, Japan, in 2010, the working group has generated new guidelines. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. To simplify the entire guidelines, we have adopted a statement format that differs from the 2006 guidelines, although the headings are similar to the previous guidelines, i.e., classification, investigation, indications for and methods of resection and other treatments, histological aspects, and methods of follow-up. The present guidelines include recent information and recommendations based on our current understanding, and highlight issues that remain controversial and areas where further research is required.

1. Introduction

Since the publication of the international consensus guidelines for management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas in 2006 [1], these entities have been drawing increasing attention. As a consequence, a considerable amount of information has been added to the literature during the subsequent 5 years. In particular, new information has been obtained regarding endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the cyst contents, the indications for resection of branch duct IPMN (BD-IPMN) have changed from rather early resection to more deliberate observation, and some reports have documented the occurrence of concomitant pancreatic ductal adenocarcinoma (PDAC) in patients with BD-IPMN. All this new knowledge makes an update of the guidelines imperative. During the 14th meeting of the International Association of Pancreatology (IAP) held in Fukuoka, Japan, in 2010, we arranged a symposium where recent progress in preoperative diagnosis and management was presented. All the speakers in the symposium, including eight initial members and six

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new members of the working group, have generated new guidelines based on an elaborate list of items to be addressed. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. We have made a series of recommendations for all items in Table 1. However, since the grades of the recommendations are low, we have avoided repetition of grade C in almost all of the items.

All the authors contributed equally to the guidelines. M. Tanaka chaired and C. Fernandez-del Castillo co-chaired this working group of the IAP, and these two authors played a major role in the preparation of the manuscript. The remaining authors are listed in alphabetical order.

Table 1
Summary of recommendations.

1. Classification
   1a. The threshold of MPD dilation, segmental or diffuse, for characterization of MD-IPMN has been lowered to >5 mm without other causes of obstruction, thereby increasing the sensitivity for radiologic diagnosis without losing specificity. MPD dilation of 5–9 mm is considered a "*worrisome feature*", while an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*".
   1b. The definition of "malignancy" of IPMNs and MCNs has been variable, hampering comparisons of data. We recommend abandoning the term carcinoma in situ in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification.

2. Investigation
   2a. CT or MRI with MRCP is recommended for a cyst of ≥1 cm to check for "*high-risk stigmata*", including enhanced solid component and MPD size of ≥10 mm, or "*worrisome features*", including cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy. All cysts with "*worrisome features*" and cysts of >3 cm without "*worrisome features*" should undergo EUS, and all cysts with "*high-risk stigmata*" should be resected. If no "*worrisome features*" are present, no further initial work-up is recommended, although surveillance is still required.
   2b. MDCT and MRCP are most useful for distinguishing BD-IPMN from other cysts by showing multiplicity and a connection to the MPD.
   2c. Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" in centers with expertise in EUS-FNA and cytological interpretation.
   2d. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.
   2e. Distinction of BD-IPMN from a small oligocystic SCN is challenging and may require EUS-FNA with cyst fluid CEA determination.

3. Indications for Resection
   3a. Resection is recommended in all surgically fit patients with MD-IPMN. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia.
   3b. The indications for resection of BD-IPMN are more conservative. "*Worrisome features*" as well as "*high-risk stigmata*" are proposed. A BD-IPMN of >3 cm without "*high-risk stigmata*" can be observed without immediate resection.
   3c. Surgical resection is recommended for all surgically fit patients with MCN. For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

4. Methods of Resection and Other Treatments
   4a. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs. Focal non-anatomic resections or anatomic resections without lymphadenectomy or splenectomy may be considered for those without suspicion of malignancy, but carry a risk of possible leakage of mucin, and higher incidences of pancreatic fistulae and recurrence. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery.
   4b. EUS-guided ethanol ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.
   4c. Multifocal BD-IPMNs carry a similar risk of malignancy to unifocal BD-IPMN. Segmental resection can be performed to remove the IPMNs at the highest oncological risk. The threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC and multifocal BD-IPMNs, but the data supporting this idea are incomplete.

Table 1 (*continued*)

5. Histological Aspects
   5a. The type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should be part of the reporting of IPMNs, with colloid carcinomas being characterized by "intestinal" differentiation and a better prognosis than tubular carcinomas.
   5b. Instead of "minimally invasive carcinoma" derived from IPMN or MCN, it would be more appropriate to stage invasive carcinomas with the conventional staging protocols and further substage the T1 category into T1a (≤0.5 cm), T1b (>0.5 cm and ≤1 cm), and T1c (1–2 cm).
   5c. The histologic subtypes of IPMN have clinicopathologic significance. The gastric type is typically low grade, with only a small percentage developing into carcinoma. However, if a carcinoma does develop, it is usually of the tubular type and aggressive. Large intestinal-type IPMNs can have invasive carcinoma of the colloid type with indolent behavior.
   5d. If clear high-grade dysplasia or invasive carcinoma is present at the margin by frozen section analysis, further resection is warranted. All patients should be informed preoperatively about the possibility of total pancreatectomy. Moderate-grade or low-grade dysplasia may not require any further therapy.
   5e. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN, being careful to identify the MPD as precisely as possible when processing the specimen.
   5f. A distinction between PDAC derived from an IPMN and PDAC concomitant with an IPMN is proposed with regard to the topological relationship and histological transition, although the distinction sometimes remains undetermined.

6. Methods of follow-up
   6a. Patients without "*high-risk stigmata*" should undergo MRI/MRCP (or CT) after a short interval (3–6 months) to establish the stability, and then annual history/physical examination, MRI/MRCP (or CT) and serologic marker surveillance. Short interval surveillance (3–9 months) should be considered for patients whose IPMN progresses toward "*high-risk stigmata*" and patients with a family history of hereditary PDAC. Some investigators continue surveillance at short intervals owing to concern over the development of distinct PDAC.
   6b. Non-invasive MCNs require no surveillance after resection. IPMNs need surveillance based on the resection margin status. If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable. The aspect of whether a margin with moderate-grade dysplasia increases recurrence is unknown. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice a year. The follow-up strategy of invasive IPMN should be identical to that for PDAC.
   6c. In patients with two or more affected first-degree relatives, the risk rapidly escalates and merits aggressive surveillance by MRI/MRCP (or CT) and EUS. "*Worrisome features*" are of more concern. If present, patients should be considered for resection if they are surgically fit. If absent, patients should be followed by MRI/MRCP (or CT) at 3-month intervals and EUS annually for the first 2 years. Patients with a rapidly growing BD-IPMN and patients who develop "*worrisome features*" should be strongly considered for resection. The interval of surveillance after 2 years of no change can be lengthened to 6 months, but no longer in view of the relatively high incidence of PDAC reported for BD-IPMN.
   6d. There are no screening recommendations for detecting extrapancreatic malignancies in patients with IPMN on surveillance and after resection, but consideration of extrapancreatic neoplasms should be made based on the frequency of these malignancies in the general population of the country or region.

2. Classification

2.1. Criteria for distinction of BD-IPMN and main duct IPMN (MD-IPMN)

IPMNs can be classified into three types, i.e., MD-IPMN, BD-IPMN, and mixed type, based on imaging studies and/or the histology (Fig. 1) [1]. MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct (MPD) of >5 mm without other causes of obstruction. According to recent reports, a low threshold for MPD dilation (5 mm) can be adopted, which increases the sensitivity for radiologic diagnosis of MD-IPMN without losing specificity [2–10]. In the revised guidelines, MPD

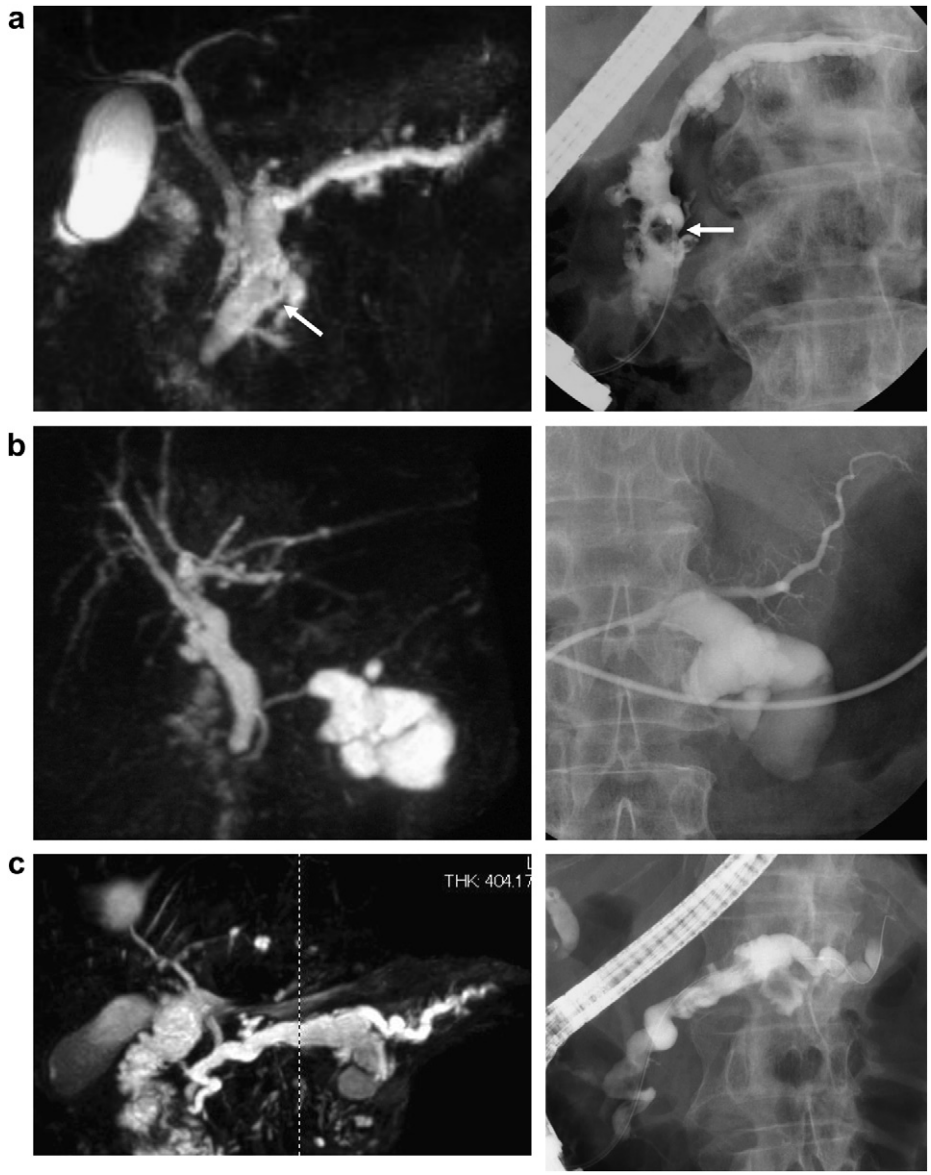


Fig. 1. MRCP (left panels) and ERCP (right panels) demonstrating the three morphological types of IPMN. a. Main duct type with a mural nodule (arrows). b. Branch duct type. c. Mixed type.

dilation of 5–9 mm is considered a "*worrisome feature*" and an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*". Pancreatic cysts of >5 mm in diameter that communicate with the MPD should be considered as BD-IPMN, with pseudocyst being in the differential diagnosis for patients with a prior history of pancreatitis. Mixed type patients meet the criteria for both MD-IPMN and BD-IPMN.

There are considerable differences in the proportions of each type and the risks of malignancy (Table 2) [2–23]. The differences are partly caused by variation in the type definitions, since the correlation between the histologic and radiologic criteria is around 70% [8,24]. While the MPD can be dilated through ductal hypertension caused by mucin, protein plugs, and focal pancreatitis, neoplastic involvement without ductal dilation can be seen histologically [25]. Since the classification is important for clinicians to plan the management, it should be based on the preoperative radiologic images, and the pathological classification can be specified a posteriori.

2.2. Definition of malignant IPMN and MCN

IPMNs and MCNs exhibit a spectrum of neoplastic transformation, both within each category and often in a given case, ranging from innocuous lesions that used to be called "hyperplasia" or adenoma (currently classified as "low-grade dysplasia") to invasive carcinomas [26,27]. The definition of "malignancy" has been variable, with most authors including "carcinoma in situ" (CIS) in the malignant category, while others reserve this term for invasive neoplasms, and yet others define "malignancy" by aggressive clinical behavior [27]. This wide variation hampers comparisons of data, and hinders determination of the significance of lesions and placement of patients into clearly defined categories. For this reason, we recommend abandoning the term CIS in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification [26].

Table 2
Frequencies of malignancy in IPMNs according to the morphological types.

Total IPMNs					Main duct type			Branch duct type			Mixed type		
First author	Year	Total number	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)
Sugiyama [11]	2003	62	34 (54.8%)	20 (32.3%)	30 (48.4%)	21 (70.0%)	17 (56.7%)	32 (51.6%)	13 (40.6%)	3 (9.4%)			
Sohn[a][12]	2004	136	>52 (38.2%)	52 (38.2%)	36 (26.5%)	>18 (50.0%)	18 (50.0%)	60 (44.1%)	>18 (30.0%)	18 (30.0%)	33 (24.3%)	>16 (48.5%)	16 (48.5%)
Salvia [13]	2004	140	83 (59.3%)	58 (41.4%)	140 (100%)	83 (59.3%)	58 (41.4%)						
Suzuki[a][14]	2004	1024	>446 (43.6%)	446 (43.6%)	201 (19.6%)	>120 (59.7%)	120 (59.7%)	509 (49.7%)	>150 (29.5%)	150 (29.5%)	228 (22.3%)	148 (64.9%)	148 (64.9%)
Lee [15]	2005	67	24 (35.8%)	9 (13.4%)	27 (40.3%)	12 (44.4%)	3 (11.1%)	35 (52.2%)	10 (28.6%)	4 (11.4%)	5 (7.5%)	2 (40.0%)	2 (40.0%)
Serikawa [2]	2006	103	41 (39.8%)	28 (27.2%)	47 (45.6%)	30 (63.8%)	21 (44.7%)	56 (54.4%)	11 (19.6%)	7 (12.5%)			
Schmidt [3]	2007	156	50 (32.1%)	29 (18.6%)	53 (34.0%)	30 (56.6%)	15 (28.3%)	103 (66.0%)	20 (19.4%)	14 (13.6%)			
Rodriguez [20]	2007	145	32 (22.1%)	16 (11.0%)				145 (100%)	32 (22.1%)	16 (11.0%)			
Schnelldorfer [16]	2008	208	82 (39.4%)	63 (30.3%)	76 (36.5%)	49 (64.5%)		84 (40.4%)	15 (17.9%)		48 (23.1%)	18 (37.5%)	
Kim [17]	2008	118	36 (30.5%)	28 (23.7%)	70 (59.3%)	25 (35.7%)	23 (32.9%)	48 (40.7%)	>3 (6.3%)	3 (6.3%)			
Nagai [4]	2008	72	44 (61.1%)	30 (41.7%)	15 (20.8%)	15 (100%)	10 (66.7%)	49 (68.1%)	25 (51.0%)	18 (36.7%)	8 (11.1%)	4 (50.0%)	2 (25.0%)
Jang [21]	2008	138	26 (18.8%)	17 (12.3%)				138 (100%)	26 (18.8%)	17 (12.3%)			
Ohno [18]	2009	87	45 (51.7%)	19 (21.8%)	14 (16.1%)	11 (78.6%)	4 (28.6%)	48 (55.2%)	20 (41.7%)	9 (18.8%)	25 (28.7%)	14 (56.0%)	6 (24.0%)
Nara [19]	2009	123	82 (66.7%)	61 (49.6%)	26 (21.1%)	26 (100%)	21 (80.8%)	59 (48.0%)	26 (44.1%)	14 (23.7%)	38 (30.9%)	30 (78.9%)	26 (68.4%)
Bournet [7]	2009	99	24 (24.2%)	14 (14.1%)				47 (47.5%)	6 (12.8%)	4 (8.5%)	52 (52.5%)	18 (34.6%)	10 (19.2%)
Hwang [5]	2010	187	58 (31.0%)	43 (23.0%)	28 (15.0%)	20 (71.4%)	17 (60.7%)	118 (63.1%)	19 (16.1%)	14 (11.9%)	41 (21.9%)	19 (46.3%)	12 (29.3%)
Mimura [6]	2010	82	54 (65.9%)	29 (35.4%)	39 (47.6%)	34 (87.2%)	19 (48.7%)	43 (52.4%)	20 (46.5%)	10 (23.3%)			
Sadakari [22]	2010	73	6 (8.2%)	1 (1.4%)				73 (100%)	6 (8.2%)	1 (1.4%)			
Kanno [23]	2010	159	40 (25.2%)	19 (11.9%)				159 (100%)	40 (25.2%)	19 (11.9%)			
Crippa [10]	2010	389	181 (46.5%)	118 (30.3%)	81 (20.8%)	55 (68%)	39 (48%)	159 (40.9%)	34 (22%)	17 (11%)	149 (38.3%)	92 (62%)	62 (42%)
Total		3568	>1440 (>40.4%)	1100 (30.8%)	883 (24.7%)	>549 (>62.2%)	385 (43.6%)	2027 (56.8%)	>494 (>24.4%)	337 (16.6%)	627 (17.6%)	>361 (>57.6%)	284 (45.3%)

Abbreviation: IPMN: intraductal papillary mucinous neoplasm.
[a] Since these reports only included invasive IPMNs, the frequency of malignant IPMNs is underestimated in this table owing to the absence of data for non-invasive IPMNs.

3. Investigation

3.1. Work-up for cystic lesions of the pancreas

Cystic lesions are increasingly being recognized by imaging studies, and the frequency of pancreatic cyst detection by MRI (19.9% [28]) is higher than by CT (1.2% [29] and 2.6% [30]). A cyst with invasive carcinoma is uncommon in patients with an asymptomatic pancreatic cyst, particularly one of <10 mm in size, and therefore no further work-up may be needed at that point, although follow-up is still recommended [31,32]. For cysts greater than 1 cm, pancreatic protocol CT or gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) is recommended for better characterization of the lesion (Fig. 2) [33]. A recent consensus of radiologists suggested dedicated MRI as the procedure of choice for evaluating a pancreatic cyst, based on its superior contrast resolution that facilitates recognition of septae, nodules, and duct communications [33]. When patients are required to undergo frequent imaging for follow-up, MRI may be better for avoiding radiation exposure.

For amelioration of symptoms, and owing to the higher risk of malignancy, all symptomatic cysts should be further evaluated or resected as determined by the clinical circumstances.

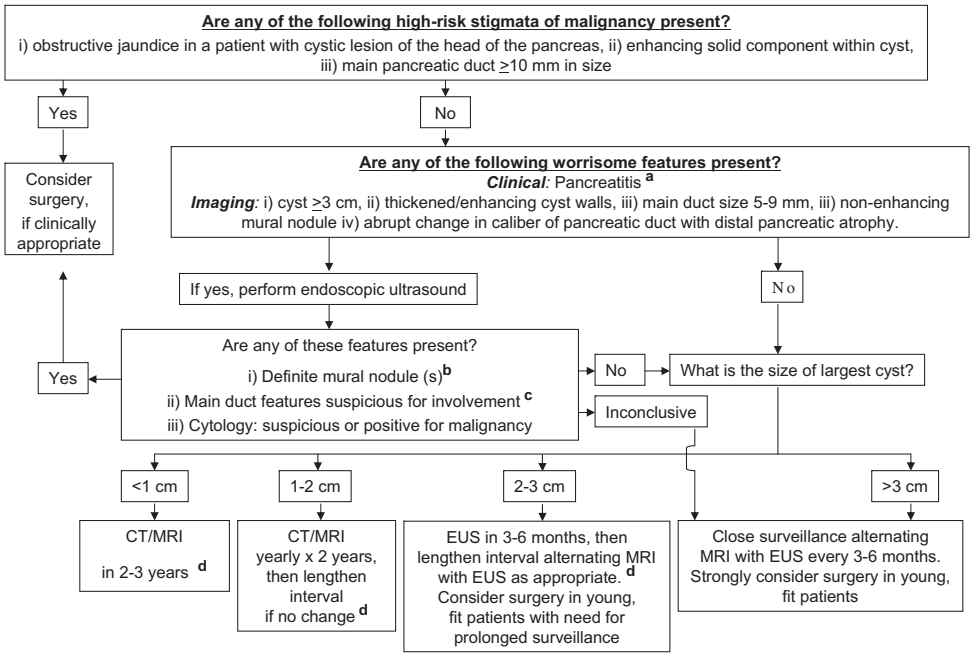
"*Worrisome features*" on imaging include cyst of ≥3 cm, thickened enhanced cyst walls, MPD size of 5–9 mm, non-enhanced mural nodules, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy [34–38].

Cysts with obvious "*high-risk stigmata*" on CT or MRI (i.e., obstructive jaundice in a patient with a cystic lesion of the pancreatic head, enhanced solid component, MPD size of ≥10 mm) should undergo resection without further testing. All smaller cysts with "*worrisome features*" should be evaluated by EUS to further risk-stratify the lesion. Patients with cysts of >3 cm and no "*worrisome features*" can also be considered for EUS to verify the absence of thickened walls or mural nodules, particularly if the patient is elderly.

All patients with cysts of ≤3 cm in size without "*worrisome features*" should undergo surveillance according the size stratification (Fig. 2) [39].

3.2. Distinction of BD-IPMN from MCN and other pancreatic cysts

Using a combination of the clinical history, sex, imaging characteristics, cytology, and cyst fluid and chemical analyses of carcinoembryonic antigen (CEA) and amylase, pancreatic cysts can not only be characterized as mucinous or non-mucinous, but also accurately identified for their specific subtypes [40–56]. A combination of the clinical and imaging characteristics provides the best initial preoperative diagnosis of the cyst type (Table 2). For an imaging diagnosis of BD-IPMN, multidetector CT (MDCT) and MRCP are the most useful primary methods for defining the morphology, location, multiplicity, and communication with the MPD. [8,9,18,57,58]. Reliable distinguishing features of BD-IPMN include multiplicity and visualization of a connection to the MPD, although such a connection is not always observed. EUS can then be used for detecting mural nodules and invasion, and is most effective for delineating the malignant characteristics (Fig. 3) [18], although it has the limitation of operator dependency [13,58]. Chemical



a. Pancreatitis may be an indication for surgery for relief of symptoms.
b. Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
c. Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is incolclusive.
d. Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Fig. 2. Algorithm for the management of suspected BD-IPMN.

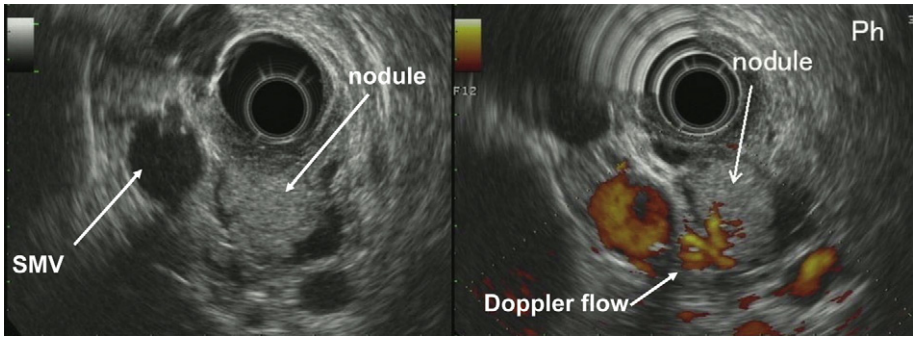


Fig. 3. EUS showing a mural nodule in the dilated MPD with Doppler flow indicating the presence of a blood supply.

analyses of the CEA and amylase levels as well as cytology of the cyst content obtained by EUS-FNA are often useful, but cannot distinguish MCN and IPMN [47,51,54–56]. A more recent study claimed that a molecular analysis for *GNAS* mutations can distinguish MCN from BD-IPMN [59].

3.3. Roles of cyst fluid analysis and cytology obtained by EUS-FNA in the diagnosis of cystic lesions of the pancreas

The use of EUS-FNA varies widely throughout the world. Elevated CEA is a marker that distinguishes mucinous from non-mucinous cysts, but not benign from malignant cysts [53–56,59–63]. A cut-off of ≥192–200 ng/ml is ~80% accurate for the diagnosis of a mucinous cyst [53–55]. An increase the cut-off value improves the specificity at the expense of the sensitivity [63]. A low CEA level does not exclude a mucinous cyst. Cyst fluid amylase is not uniformly elevated in IPMN, and MCN may also exhibit elevated amylase levels [53]. Serous cysts typically have low levels of both CEA and amylase. Cytology can be diagnostic, although the sensitivity is limited by the scant cellularity [50,51,63–71]. In summary, interpreting the results of biochemical markers in cyst fluid is a complex exercise in pattern recognition, and should be reserved for patients in whom additional information will have an impact on the surgical decision-making.

In centers with expertise in EUS-FNA and cytological interpretation, cytological analysis adds value, especially for evaluation of a small BD-IPMN without "*worrisome features*" [56]. "High-grade epithelial atypia" recognizes epithelial cells with cellular atypia that is qualitatively and quantitatively insufficient for a malignant interpretation, and may be a more sensitive predictor of malignancy than positive cytology [3,51,56,72,73]. Such cells in the cyst fluid predicted malignancy in a mucinous cyst with 72% sensitivity and positive predictive value (80% accuracy) in one study [51], and detected 30% more cancers in small IPMN than "*worrisome features*" in another study [56].

Molecular analyses of the cyst fluid for diagnosis are still evolving. Studies show that detection of *KRAS* mutations more accurately supports a mucinous rather than malignant cyst [45–47]. A recent study indicates that *GNAS* mutations may be helpful in distinguishing significant mucinous cysts from indolent cysts that can be conservatively managed [59].

It is important to highlight that Japanese investigators do not recommend cyst fluid analysis for the diagnosis of mucinous-like cystic lesions, and believe that a cyst of any size with "*worrisome features*" should not be aspirated, because it may cause leakage of the cyst content, possibly leading to peritoneal dissemination [74,75]. At present, EUS-FNA with cytological and molecular analyses is still considered investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" only in centers with expertise in EUS-FNA and cytological interpretation.

3.4. Role of cytology and/or analysis of the pancreatic juice in the diagnosis of malignant BD-IPMN

Pancreatic juice can be obtained via endoscopic retrograde cholangiopancreatography (ERCP) by washing or brushing for cytology. Pancreatic juice can also be obtained from the MPD or a dilated branch duct affected by IPMN, although selective cannulation may be difficult. Only a few reports mention pancreatic juice cytology of BD-IPMN, with variable yields [70,76]. One large series showed a significant role of CEA levels of >30 ng/ml in diagnosing malignant BD-IPMN [77]. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.

3.5. Distinction of BD-IPMN from serous cystic neoplasm (SCN)

Serous cystadenomas have three morphological patterns: polycystic, honeycomb, and oligocystic. BD-IPMN can be properly distinguished from SCN with a polycystic or honeycomb pattern by either CT or MRCP [55,74,78,79] (Table 3). The differentiation between a small oligocystic SCN and a BD-IPMN is challenging and may require EUS-FNA with cyst fluid CEA determination [80–82].

4. Indications for resection

4.1. Indications for resection of MD-IPMN

According to published series of ≥50 cases (Table 2), the mean frequency of malignancy in MD-IPMN is 61.6% (range, 36–100%) and the mean frequency of invasive IPMN is 43.1% (range, 11–81%) [2–6,11–19]. Considering these high incidences of malignant/invasive lesions and the low 5-year survival rates (31–54%) [3–5,12–14], surgical resection is strongly recommended for all surgically fit patients. However, MPD dilation of 5–9 mm should be considered as one of the "*worrisome features*", similar to the case for BD-IPMN (Fig. 2), with a recommendation of evaluation but no immediate resection. To date, there have been no consistent predictive factors for malignancy in MD-IPMN, including the degree of MPD dilation, presence of symptoms, or mural nodules [5,11,13].

The aim of resection is to achieve complete removal of a tumor with a negative margin. In the segmental ectatic type or diffuse type with focal lesions (mural nodules or combined branch lesions, etc.), it is relatively easy to determine the resection side (proximal or distal pancreatectomy) and transection line.

Table 3
Typical clinical and imaging features of common pancreatic cysts.

Characteristic	MCN	BD-IPMN	SCN	Pseudocyst
Sex (% female)	>95%	~55%	~70%	<25%
Age (decade)	4th, 5th	6th, 7th	6th, 7th	4th, 5th
Asymptomatic	~50%	Mostly when small	~50%	Nearly zero
Location (% body/tail)	95%	30%	50%	65%
Common capsule	Yes	No	Yes	N/A
Calcification	Rare, curvilinear in the cyst wall	No	30–40%, central	No
Gross appearance	Orange-like	Grape-like	Spongy or honeycomb-like	Variable
Multifocality	No	Yes	No	Rare
Internal structure	Cysts in cyst	Cyst by cyst	Microcystic and/or macrocystic	Unilocular
Main pancreatic duct communication	Infrequent	Yes (though not always demonstrable)	No	Common
Main pancreatic duct	Normal or deviated	Normal, or dilated to >5 mm, suggesting combined type	Normal or deviated	Normal or irregularly dilated, may contain stones

Abbreviations: MCN, mucinous cystic neoplasm; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; SCN, serous cystic neoplasm; N/A, not applicable.

In the diffuse dilation type without focal lesions, more careful evaluation is warranted, including ERCP. Some of these patients may not even have IPMN, but rather chronic pancreatitis. A dilated papilla with mucin extrusion and/or a mural nodule visualized by ERCP definitely confirms the diagnosis of MD-IPMN. If indeed IPMN is diagnosed, right-sided pancreatectomy is preferred because it is technically easier to resect additional pancreatic tissue to achieve a negative margin.

Frozen biopsy sections are useful for deciding the resection line [83]. If the resection margin is positive for high-grade dysplasia, additional resection of the pancreas should be attempted to obtain a negative margin. If low-grade or moderate-grade dysplasia is found, further resection is controversial [84–87]. Total pancreatectomy should be applied selectively in younger patients who can handle the complexities of brittle diabetes and exocrine insufficiency [88,89]. Intraductal ultrasonography (Fig. 4), pancreatoscopy (Fig. 5), and cytology have been used to obtain additional information of the surgical margin in difficult cases [90,91]. However, all of these investigations should preferably be performed preoperatively to avoid leakage of mucin.

4.2. Indications for resection of BD-IPMN

The mean frequency of malignancy in resected BD-IPMN is 25.5% (range, 6.3–46.5%) and the mean frequency of invasive cancer is 17.7% (range, 1.4–36.7%) (Table 2) [2–7,11–23]. Although resection of BD-IPMN therefore warrants consideration, these lesions mostly occur in elderly patients, and the annual malignancy rate is only 2–3% [92,93]. These factors support conservative management with follow-up in patients who do not have risk factors predicting malignancy. The usefulness of the previous consensus criteria for resection [1] has been validated by many reports [5–8,22–24,94,95]. New high-risk factors proposed include a rapidly increasing cyst size [92,96] and high-grade atypia rather than "positive" cytology [51,56,65,67,72].

Although still controversial, younger patients (<65 years) with a cyst size of >2 cm may be candidates for resection owing to the cumulative risk of malignancy [21,97]. The decision needs to be individualized and to depend not only on the risk of malignancy but also on the patient's conditions and cyst location. Since a BD-IPMN size of >3 cm is a weaker indicator of malignancy than the presence

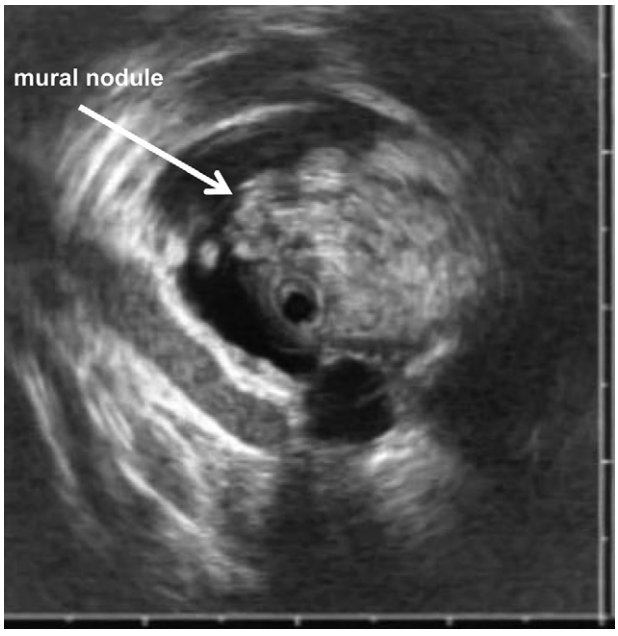


Fig. 4. Intraductal ultrasonogram demonstrating a 25-mm mural nodule in the MPD.

Fig. 5. Peroral pancreatoscopic photograph showing a fish egg-like mucosal lesion in the MPD.

of mural nodules and positive cytology, BD-IPMN of >3 cm without these signs can be observed without immediate resection, particularly in elderly patients.

4.3. Indications for resection of MCN

MCN defined by the presence of ovarian stroma has a low prevalence of invasive carcinoma (<15%) with no malignancy in MCNs of <4 cm without mural nodules [40,98]. Observation may be considered in elderly frail patients [40]. However, given the relatively young age of most patients, the risk of progression to invasive MCN, and their common locations in the pancreatic body and tail, surgical resection is recommended for all surgically fit patients, since the natural history of MCN is still unknown and nonoperative management would require years of follow-up based on high-resolution imaging associated with high costs [40,98–100]. Patients with invasive MCN are significantly older (by 11 years) than those with non-invasive MCN, [98–100], and frequently contain areas of low-grade dysplasia [40,98,99], suggesting that we are presently unable to securely identify invasive MCN. Resection is routinely curative in non-invasive MCN with no recurrence [40,98].

MCNs are usually located in the pancreatic body and tail, and thus require distal pancreatectomy that can be performed safely at high-volume centers [101,102]. In patients with MCNs of <4 cm without mural nodules, parenchyma-sparing resections (i.e. middle pancreatectomy) and distal pancreatectomy with spleen preservation as well as laparoscopic procedures should be considered [102,103].

5. Methods of resection and other treatments

5.1. Methods of pancreatectomy for invasive and non-invasive MCNs and IPMNs

Although preoperative and intraoperative assessment of the dysplasia grades of MCNs and IPMNs can be difficult, US, CT, MRI, and EUS will identify most tumors with a significant invasive component [104]. In such patients, pancreatoduodenectomy, left pancreatectomy, or total pancreatectomy according to the site and extent of the disease with lymph node dissection remains the standard treatment [105,106]. Limited resections or even focal non-anatomic resections (excision, enucleation, uncinatectomy) may be considered for MCN or BD-IPMN without clinical, radiologic, cytopathologic, or serologic suspicion of malignancy [107–124]. However, non-anatomic resections may be associated with rare, but possible, leakage of mucin followed by pseudomyxoma peritonei [125,126], and also have a higher incidence of pancreatic fistulae and risk of recurrence from potentially residual neoplasm. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery [127–129]. Conversion to a standard resection with lymphadenectomy should occur if intraoperative findings raise concern for malignancy or frozen-section pathology reveals high-grade dysplasia or invasive disease. When the final pathology reveals invasion or positive margin for high-grade dysplasia undetected on frozen sections, a reoperation should be performed in surgically fit patients.

5.2. Role of mucosal ablation by ethanol injection under EUS guidance in the management of MCN or IPMN

Investigators have begun exploring the possibility of EUS-guided ablation of pancreatic cysts by ethanol or ethanol followed by paclitaxel [130–132]. Preferred candidates include (1) patients with cystic lesions of >2 cm, either unilocular or oligolocular, that show no communication with the MPD, and (2) cysts in patients who refuse surgery or are high-risk surgical candidates [133,134]. The reported short-term CT-defined cyst resolution rates were 33–79% [131–135], and variable histopathologic degrees of epithelial ablation were observed in the resected specimens [131,133,135]. DeWitt et al. [134] reported that follow-up by CT revealed no evidence of cyst recurrence for a median of 26 months after cyst resolution. Complications include acute pancreatitis (4.5–10%), abdominal pain (<20%), and splenic vein obliteration [131,133,135].

Although the procedure may be promising, there are some problems that remain to be addressed, including insufficient ethanol infiltration and impossible imaging surveillance after the cyst collapse [129]. Moreover, recent studies have shown that PDAC occurs quite frequently not only as malignant transformation of IPMN but also in other sites separate from IPMN [39,136–138]. More research needs to be carried out on the techniques, materials, long-term outcomes, and adequacy of this procedure. At present, EUS-guided ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.

5.3. Approach to multifocal BD-IPMN

IPMN probably represents a pancreatic “field defect”, i.e., all pancreatic ductal epithelial cells are at risk of dysplastic change, and this can be apparent in patients with multifocal (two or more) BD-IPMNs (Fig. 6). Current series estimate that 25–41% of all BD-IPMNs are multifocal [3,8,20]. There is no convincing evidence that the risk of invasive IPMN multiplies according to the number of lesions. In fact, in one series, patients with symptomatic unifocal BD-IPMN carried a higher risk than those with symptomatic multifocal BD-IPMNs (18% versus 7%) [3].

The treatment approach to multifocal BD-IPMNs should mirror that of unifocal BD-IPMN. When resection is indicated, segmental anatomic pancreatectomy should be performed in cases where the multifocal disease is limited to a pancreatic region. In some cases, the disease may not be able to be eliminated without total pancreatectomy. Even then, it is reasonable to perform a segmental resection to remove the IPMNs at the highest oncological risk and perform surveillance of the remaining lesions. However, the threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC, because of the increased prevalence of higher-grade lesions [139].

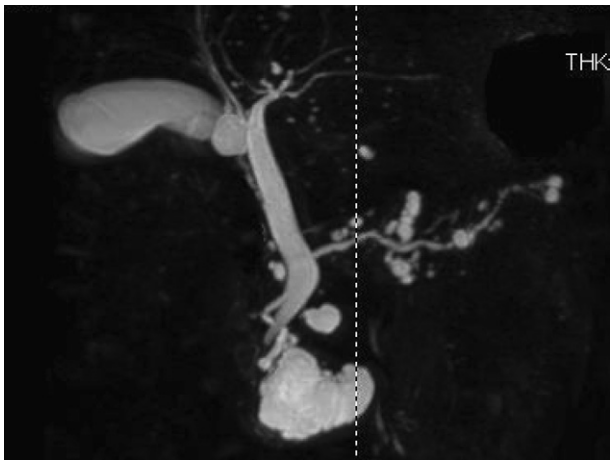


Fig. 6. MRCP demonstrating multifocal BD-IPMNs.

6. Histological aspects

6.1. Types of invasive carcinoma of malignant IPMN

It is now well established that the type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should therefore be part of the reporting of IPMNs [140–143]. Colloid carcinomas are characterized by "intestinal" differentiation, evidenced by diffuse and specific expression of CDX2 and MUC2, and have a better prognosis than tubular carcinomas [142]. It is conceivable that these histological differences may drive the use of distinct adjuvant chemotherapy protocols, although this has not yet been evaluated.

6.2. Pathologic definition of minimally invasive carcinoma derived from IPMN or MCN

6.2.1. Staging of invasive carcinomas (definition of "minimally invasive carcinoma")

Since the term "minimally invasive" has been variably defined by different authors [144–147], it is preferable to avoid such a non-specific term. Instead, it would be more appropriate to stage invasive carcinomas with conventional staging protocols including the AJCC/TNM [148], and then further substage the T1 category (those with invasive carcinomas of <2 cm) into T1a for those that are ≤ 0.5 cm, T1b for those that are >0.5 cm and ≤ 1 cm, and T1c for those that are 1–2 cm. This substaging of T1 conforms to the methods that are being employed for other organs and tumor types, allows the collection of more accurate and comparable data for future evaluation, and is in accordance with the recent proposal made by Furukawa et al. [149].

6.3. Distinction and clinical relevance of gastric, intestinal, pancreatobiliary, and oncocytic forms of IPMNs

The cell lineage of the "papillary component" of IPMNs has clinicopathologic significance (Fig. 7) [142,147,149–153]. The vast majority of BD-IPMNs are of the gastric type, which is MUC5AC-positive but MUC1-negative, with MUC2 highlighting only the scattered goblet cells. The gastric type is typically low grade, with only a small percentage developing into carcinoma, although if a carcinoma does develop in these patients, it is usually of the tubular type and behaves like a conventional PDAC [151,153]. A significant portion of MD-IPMNs are of the intestinal type, showing diffuse expression of CDX2 and MUC2. Large and complex intestinal-type IPMNs can have invasive carcinoma, typically of the colloid type (CDX2/MUC2-positive) and with relatively indolent behavior [142]. The oncocytic type is defined by complex arborizing papillae with delicate cores, oncocytic cells, and intraepithelial lumina formation, and common MUC6 expression [154,155]. This type tends to be large, with a more obscure intraductal nature and relatively uncommon and limited invasion, and most cases receive a clinical diagnosis of "cystadenocarcinoma" [156]. The pancreatobiliary type is the least well characterized and the least common, and is regarded by some as a high-grade version of the gastric type. Invasive carcinoma associated with this type is usually tubular and aggressive [150].

Based on the clinical associations described above, it is sometimes feasible to predict the subtypes preoperatively. In a preoperative biopsy, EUS-guided or otherwise, it may be possible to employ this subclassification, provided that the papillary component of the tumor is sampled. One study obtained consistent subclassifications in 15 of 19 patients (79%) by preoperative sampling of the pancreatic juice via endoscopy [157].

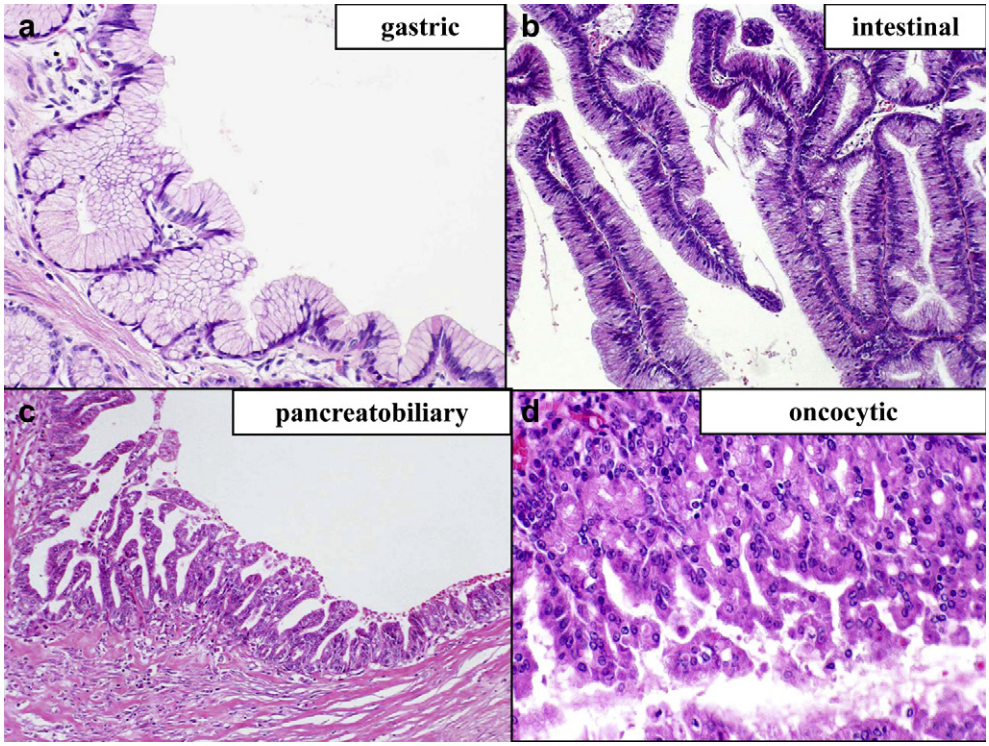


Fig. 7. Histological subclassification of IPMNs. a. The gastric type shows tall columnar cells with basally oriented nuclei and abundant pale mucinous cytoplasm. b. The intestinal type is composed of tall papillae lined by columnar cells with pseudostratified nuclei and basophilic cytoplasm with variable amounts of apical mucin. c. The pancreatobiliary type has thin branching papillae with high-grade dysplasia. The cells are cuboidal and have round hyperchromatic nuclei, prominent nucleoli, and moderately amphophilic cytoplasm with a less mucinous appearance. d. The oncocytic type usually exhibits complex arborizing papillae lined by two to five layers of cuboidal to columnar cells with large, round, fairly uniform nuclei containing single, prominent, eccentrically located nucleoli, and abundant eosinophilic granular cytoplasm sometimes in a cribriform or solid growth pattern.

6.4. Role of intraoperative frozen section evaluation in the surgical management of IPMNs

IPMNs can be ill-defined owing to the spread to branch ducts and smaller ductules. Therefore, the assessment of adequate margins may have to rely upon frozen section analysis [83,86,158,159]. However, frozen sections are a suboptimal method for analyzing tissue morphology, and should be used cautiously. If clear high-grade dysplasia or invasive carcinoma is present at the margin, further resection is warranted. Similarly, if exuberant papillary nodules are present at the margin, there may be abundant residual tumor in the pancreas [164]. All patients should be informed preoperatively that the resection may possibly be extended to total pancreatectomy. In contrast, the presence of lesser grades of dysplasia (moderate or low-grade) may not require any further therapy [141].

The common incidental occurrence of pancreatic intraepithelial neoplasia (PanIN)-1 and -2 in the general population may show up in frozen sections of the margin. Since low-grade PanINs can be indistinguishable from low-grade IPMNs [160], it may be preferable to report that "no in situ or invasive carcinoma is identified; intraductal/intraepithelial neoplasm of low/moderate grade, either PanIN or low-grade IPMN, is present". In addition, a section of the margin may show nothing but inflammation and denuded epithelium. The pathologist cannot render a diagnosis without an intact epithelium, and this should be reported as "denuded epithelium and inflammation", with such cases being carefully analyzed clinically because the denudation may prove to be the presence of an adjacent tumor [161].

6.5. Special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN

Dilation of the MPD and neoplasia of the duct lining are not always correlated. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN according to the distribution of the neoplasm. There are no special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN. The most important points are to identify the MPD as precisely as possible when processing the specimen, to sample the cystic lesion completely, and to examine the resected specimen thoroughly. There are different approaches to the dissection of these specimens [27,162].

6.6. Distinction of carcinoma derived from and concomitant with an IPMN

PDAC may develop independently in the pancreatic duct separately from an IPMN [39,163,164]. When PDAC originates in the vicinity of an IPMN, the distinction between PDAC derived from the IPMN and PDAC concomitant with the IPMN is sometimes difficult. Definitions of these conditions were proposed by the Japan Pancreas Society, mainly with regard to the topological relationship and histological transition between IPMN and PDAC [163]. Among 765 patients with resected IPMN, there were 183 patients with invasive carcinoma (24%). Of these, 122 (66%) were classified as PDAC derived from IPMN, 31 (17%) as PDAC concomitant with IPMN because the two lesions were discontinuous, and 30 (16%) as undetermined. It is also imperative to make every effort to distinguish between a retention cyst occurring from PDAC and IPMN accompanying PDAC. Retention cysts may be lined with epithelium with regenerative atypia or even by cancer cells extending from the PDAC, whereas IPMN is characterized by dilated pancreatic ducts lined with dysplastic mucinous epithelium showing micropapillary or macropapillary projections.

7. Methods of follow-up (Fig. 2)

7.1. Follow-up of non-resected IPMN

The decision to follow an IPMN is a matter of clinical judgment based on the patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference. There is little evidence in the literature to guide the frequency and type of surveillance for IPMNs.

At baseline, history/physical examination and MRI/MRCP (or pancreatic protocol CT) surveillance, and EUS when the presence of a mural nodule is suspected, are recommended. If the expertise is available, consideration may be given for EUS with cytopathology [3,51,71–73], CEA, [46,55,165], and molecular analyses [46,165–167].

For surveillance, patients without "*high-risk stigmata*" should undergo short interval (3–6 months) pancreatic MRI/MRCP (or CT) to establish the stability, if prior imaging is not available. Subsequently, surveillance should be performed according to the size stratification (Fig. 2). There are no good long-term data to indicate whether surveillance can be safely spaced to every 2 years or even discontinued after long-term stability. Concern over the development of PDAC in the pancreas harboring IPMN has prompted some investigators to continue surveillance at short intervals [39,136–138,163,164,168–173].

If surgically fit, patients with "*high-risk stigmata*" detected on surveillance should undergo resection. Shorter interval surveillance (3–9 months) should be considered in patients whose IPMN progresses toward these indicators or patients who already have "*high-risk stigmata*" and, for reasons of operative risk or personal preference, have chosen heightened surveillance over resection. The issue of whether a rapid growth rate is correlated with an increased risk of malignancy remains unclear, but shorter interval surveillance is recommended in such patients [92].

7.2. Follow-up of surgically resected IPMN and MCN

7.2.1. Recurrence of MCN following resection

MCNs are almost always solitary and complete resection of a non-invasive MCN is curative, thus necessitating no postoperative surveillance [74,98–100,174–176]. Although patients with invasive MCN have a poorer prognosis [98,100,174–176], the interval to follow-up imaging should match that of PDAC, despite a lack of proof that surveillance imaging improves the prognosis compared with a strategy based on symptom recurrence.

7.2.2. Follow-up and recurrence of IPMN following resection

Clinically relevant residual IPMN lesions may persist in patients postoperatively because (1) a known BD-IPMN was left unresected, (2) the surgical margins were found to have residual IPMN, and/or (3) new lesions developed in the remnant pancreas. Again, some investigators continue surveillance at short intervals owing to concern over the development of PDAC in the pancreas after resection of IPMN [39,136–138,163,164,168–173].

a) *Known IPMN in the remnant pancreas*: Patients with multifocal BD-IPMNs may have known IPMN in the remaining pancreas following IPMN resection. These patients should be followed as non-resected IPMNs (Item 7-1).

b) *Postoperative follow-up based on the resection margin status*: The resection margin may show (1) normal pancreatic tissue, (2) non-dysplastic changes (PanIN-1A or -1B), (3) low-grade dysplasia, (4) moderate-grade dysplasia, (5) high-grade dysplasia, or (6) invasive carcinoma [83].

1, 2) Normal columnar or mucinous metaplasia (PanIN-1A or -1B) should be considered as negative margins [86]. Such patients should undergo follow-up as per the guidelines for unresected

IPMN, if any, in the remnant pancreas (Item 4-2). If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence (see below).

3–5) It is unclear whether a margin that is microscopically positive for moderately dysplastic IPMN increases IPMN recurrence. For patients with low-grade or moderate-grade dysplasia at the margin, there is little evidence to guide the frequency and type of surveillance required to detect IPMN recurrence. We suggest that history/physical examination and MRCP surveillance are performed twice a year in cases of non-invasive IPMN following resection, and perhaps more often if symptoms, signs, radiographic findings, or cytopathology dictate a shorter interval of surveillance [173].

c) *New postoperative IPMN recurrence*: The rate of new recurrence of non-invasive IPMN following resection is difficult to determine from the literature, because MPD dilation in the distal pancreas following resection may be secondary to anastomotic stenosis or caused by true IPMN recurrence, and better imaging in the postoperative setting may reveal a previously undetected IPMN.

Despite these limitations, the recurrence rates in the first 5 years were reported to be 0–20% [4,85,86,177–181]. If there are no residual lesions and the margins are negative, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence, although this guidance is not evidence-based. Several recent reports of distinct PDAC development in patients with BD-IPMN suggest that CT or MRCP at 6-month intervals is appropriate for surveillance, in view of the 0.7–0.9% yearly risk of PDAC development [39,136–138,163,164,168–173].

7.2.3. Recurrence of invasive IPMN following resection

The prognosis of invasive IPMN is globally better than that of conventional PDAC. However, in cases of stage II/III invasive IPMN, the prognosis is similar to that of PDAC [16,182,183]. The follow-up strategy should be identical to that for PDAC.

7.3. Possible occurrence of PDAC in patients with IPMN on follow-up and impact of family history of PDAC

Very little evidence exists to guide the management of patients with an IPMN and a family history of PDAC. Therefore, recommendations regarding the care of these individuals must draw upon what is known for familial PDAC. The risk of an individual developing PDAC based on family history alone has been well established [184,185]. An individual with one first-degree relative with PDAC has a 2.3-fold increased risk. The risk increases to 6.4-fold with two affected first-degree relatives and 32-fold with three affected first-degree relatives. A risk prediction calculator called PancPRO is available free online at http://astor.som.jhmi.edu/BayesMendel/pancpro.html [186]. In some individuals, the actual genetic defect is known and forms part of a described syndrome. The best characterized genetic defects include *BRCA2*/Fanconi anemia pathway defects (relative risk, 3.5–10-fold [187,188]), familial atypical mole malignant melanoma (FAMMM) syndrome (relative risk, 9–47-fold [189–191]), and Peutz–Jeghers syndrome (relative risk, 132-fold [192]).

The initial assessment of an IPMN should include a detailed family history and an estimate of the relative risk of developing PDAC based on the above sources. Patients with one affected first-degree relative can be followed closely using the same criteria for patients without a family history. For individuals with two or more affected first-degree relatives, the risk rapidly escalates and merits more aggressive surveillance, but does not necessarily require a recommendation for resection. In this risk category, patients with a newly diagnosed BD-IPMN should undergo high-quality MRI/MRCP or CT and EUS. In addition to "*malignant stigmata*", "*worrisome features*" are of more concern. If present, resection should be considered if the patient is surgically fit. If absent, the patient should be followed by MRI/MRCP or CT at 3-month intervals and EUS annually for the first 2 years to evaluate the development of "*worrisome features*". Patients with a cyst that shows rapid growth or develops "*worrisome features*" should be strongly considered for resection.

7.4. Possible occurrence of malignant neoplasms in other organs in patients with IPMN on follow-up

Synchronous and metachronous occurrence of malignant diseases in extrapancreatic organs in patients with IPMNs has an incidence of 20–30% [193]. Most reports describe the occurrence of malignant conditions as a part of the patient's past history [194]. However, extrapancreatic malignancies can occur even after resection of an IPMN. Therefore, attention should be paid to this phenomenon even after resection of an IPMN.

The frequency and location of extrapancreatic malignancies differ from country to country. Gastrointestinal cancer is common in Asia [195,196], while skin, breast, and prostatic cancers are frequent in the United States [197,198]. These facts may indicate that extrapancreatic malignancies occur depending on the incidences of cancer in the general populations in different regions [194].

The relationships between the types of IPMN and extrapancreatic malignancies are controversial. Some authors reported that extrapancreatic malignancies occur in all types of IPMN [194], while others reported that transcription of MUC2 may be related to the synchronous extrapancreatic gastrointestinal cancer development seen with IPMN [199].

At present, there are no screening recommendations for detecting extrapancreatic malignancies, but once the diagnosis is made, consideration of extrapancreatic neoplasms should be undertaken based on the frequency of malignancies in the general population of the country or region. Two reports have recommended screening of colorectal polyps and cancer in the United States [198,200].

8. Conclusions

Our understanding of IPMNs of the pancreas continues to evolve. Although many new publications are available since the first guidelines were published 6 years ago, the vast majority of the data are retrospective and uncontrolled, and long-term follow-up has been limited, meaning that our knowledge of the natural history of this disease is still incomplete. In this revision, the criterion for characterizing MD-IPMN has been lowered to MPD dilation of >5 mm, without losing specificity for radiologic diagnosis. "*High-risk stigmata*" and "*worrisome features*" have been defined to stratify the risk of malignancy in BD-IPMN and consider resection or increased frequency of surveillance. Resection is still recommended in all surgically fit patients with MD-IPMN or MCN. The indications for resection of BD-IPMN are more conservative. BD-IPMNs of >3 cm without "*high-risk stigmata*" can be observed without immediate resection. Methods and intervals of surveillance are proposed with an algorithm in view of "*high-risk stigmata*" and "*worrisome features*". The issue of whether the interval of surveillance can be lengthened after 2 years of no change is controversial. Some authors advocate continuation of surveillance every 6 months in view of the relatively high incidence of PDAC in patients with BD-IPMN. For MCNs of <4 cm without mural nodules, laparoscopic as well as limited resections should be considered. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs, while limited resections without lymphadenectomy or splenectomy are

reserved for those without suspicion of malignancy. The histologic types of invasive carcinoma, colloid versus tubular, and subtypes of IPMNs have prognostic implications. During resection, frozen section analysis of the surgical margin is required to ensure there is no high-grade dysplasia or invasive cancer. IPMNs need post-operative surveillance based on the resection margin status. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice yearly.

References

[1] Tanaka M, Chari S, Adsay V, Fernández-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.

[2] 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.

[3] 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. discussion 651–654.

[4] 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. discussion 279–280.

[5] Hwang DW, Jang JY, Lee SE, Lim CS, Lee KU, Kim SW. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. Langenbecks Arch Surg 2012;397:93–102.

[6] Mimura T, Masuda A, Matsumoto I, Shiomi H, Yoshida S, Sugimoto M, et al. Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. J Clin Gastroenterol 2010;44:e224–229.

[7] Bournet B, Kirzin S, Carrere N, Portier G, Otal P, Selves J, et al. Clinical fate of branch duct and mixed forms of intraductal papillary mucinous neoplasia of the pancreas. J Gastroenterol Hepatol 2009;24:1211–7.

[8] 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.

[9] Kawamoto S, Lawler LP, Horton KM, Eng J, Hruban RH, Fishman EK. MDCT of intraductal papillary mucinous neoplasm of the pancreas: evaluation of features predictive of invasive carcinoma. Am J Roentgenol 2006;186:687–95.

[10] Crippa S, Fernández-del Castillo C, Salvia R, Finkelstein D, Bassi C, Domingues I, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clin Gastroenterol Hepatol 2010;8:213–9.

[11] Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg 2003;90:1244–9.

[12] 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. discussion 797–799.

[13] 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. Ann Surg 2004;239:678–87.

[14] Suzuki Y, Atomi Y, Sugiyama M, Isaji S, Inui K, Kimura W, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. Pancreas 2004;28: 241–6.

[15] 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.

[16] 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. discussion 646.

[17] 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.

[18] Ohno E, Hirooka Y, Itoh A, Ishigami M, Katano Y, Ohmiya N, et al. Intraductal papillary mucinous neoplasms of the pancreas: differentiation of malignant and benign tumors by endoscopic ultrasonography findings of mural nodules. Ann Surg 2009;249:628–34.

[19] Nara S, Onaya H, Hiraoka N, Shimada K, Sano T, Sakamoto Y, et al. Preoperative evaluation of invasive and noninvasive intraductal papillary-mucinous neoplasms of the pancreas: clinical, radiological, and pathological analysis of 123 cases. Pancreas 2009;38:8–16.

[20] 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.

[21] Jang JY, Kim SW, Lee SE, Yang SH, Lee KU, Lee YJ, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? Ann Surg Oncol 2008;15: 199–205.

[22] Sadakari Y, Ienaga J, Kobayashi K, Miyasaka Y, Takahata S, Nakamura M, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. Pancreas 2010;39:232–6.

[23] Kanno A, Satoh K, Hirota M, Hamada S, Umino J, Itoh H, et al. Prediction of invasive carcinoma in branch type intraductal papillary mucinous neoplasms of the pancreas. J Gastroenterol 2010;45:952–9.

[24] Baiocchi GL, Portolani N, Missale G, Baronchelli C, Gheza F, Cantù M, et al. Intraductal papillary mucinous neoplasm of the pancreas (IPMN): clinico-pathological correlations and surgical indications. World J Surg Oncol 2010;8:25 [online].

[25] Fernández-del Castillo C. Intraductal papillary mucinous neoplasms of the pancreas: a plea for prospective differentiation between main-duct and side-branch tumors. Ann Surg Oncol 2005;12:98–9.

[26] Adsay NV, Fukushima N, Furukawa T, Hruban RH, Klimstra DS, Kloppel G, et al. Intraductal neoplasm of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of digestive system. Lyon: WHO Press; 2010. p. 304–13.

[27] Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. In: Silverberg SG, editor. AFIP Atlas of tumor pathology series 4, vol. 6. Washington: ARP Press; 2007. p. 75–110.

[28] Zhang XM, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: Depiction on single-shot fast spin-echo MR images. Radiology 2002;223: 547–53.

[29] Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeeb A, Komorowski RA, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg 2004;239: 651–9.

[30] Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol 2008;191:802–7.

[31] Das A, Wells CD, Nguyen CC. Incidental cystic neoplasms of pancreas: what is the optimal interval of imaging surveillance? Am J Gastroenterol 2008;103: 1657–62.

[32] Fernández-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg 2003;138. 427–423; discussion 433–434.

[33] Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: White paper of the ACR incidental findings committee. J Am Col Radiol 2010;7:754–73.

[34] Bassi C, Crippa S, Salvia R. Intraductal papillary mucinous neoplasms (IPMNs): is it time to (sometimes) spare the knife? Gut 2008;57:287–9.

[35] Brounts LR, Lehmann RK, Causey MW, Sebesta JA, Brown TA. Natural course and outcome of cystic lesions in the pancreas. Am J Surg 2009;197:619–23.

[36] Javle M, Shah P, Yu J, Bhagat V, Litwin A, Iyer R, et al. Cystic pancreatic tumors (CPT): predictors of malignant behavior. J Surg Oncol 2007;95:221–8.

[37] Lee SH, Shin CM, Park JK, Woo SM, Yoo JW, Ryu JK, et al. Outcomes of cystic lesions in the pancreas after extended follow-up. Dig Dis Sci 2007;52: 2653–9.

[38] Salvia R, Crippa S, Falconi M, Bassi C, Guarise A, Scarpa A, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate? Gut 2007;56:1086–90.

[39] Tanaka M. Controversies in the management of pancreatic IPMN. Nat Rev Gastroenterol Hepatol 2011;8:56–60.

[40] Reddy RP, Smyrk TC, Zapiach M, Levy MJ, Pearson RK, Clain JE, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol 2004;2:1026–31.

[41] Fukushima N, Mukai K. Pancreatic neoplasms with abundant mucus production: emphasis on intraductal papillary-mucinous tumors and mucinous cystic tumors. Adv Anat Pathol 1999;6:65–77.

[42] Itai Y, Minami M. Intraductal papillary-mucinous tumor and mucinous cystic neoplasm: CT and MR findings. Int J Gastrointest Cancer 2001;30:47–63.

[43] Kimura W. IHPBA in Tokyo surgical treatment of IPMT vs MCT: a Japanese experience. J Hepatobiliary Pancreat Surg 2002;2003(10):156–62.

[44] Solcia E, Capella C, Klöppel G. Tumors of the pancreas. In: Rosai J, editor. Atlas of tumor pathology. 3rd ed., vol. 20. Washington, D.C: Armed Forces Institute of Pathology; 1997.

[45] Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol 2005;3:967–73.

[46] Khalid A, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc 2009;69:1095–102.

[47] Shen J, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. Cancer 2009;117:217–27.

[48] Sahani DV, Lin DJ, Venkatesan AM, Sainani N, Mino-Kenudson M, Brugge WR, et al. Multidisciplinary approach to diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas. Clin Gastroenterol Hepatol 2009;7:259–69.

[49] Sahani DV, Kadavigere R, Saokar A, Fernández CC, Brugge WR, Hahn PF. Cystic pancreatic lesions: a simple imaging-based classification system for guiding management. Radiographics 2005;25:1471–84.
[50] Pitman MB, Deshpande V. Endoscopic ultrasound-guided fine needle aspiration cytology of the pancreas: a morphological and multimodal approach to the diagnosis of solid and cystic mass lesions. Cytopathology 2007;18: 331–47.
[51] Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, Mino-Kenudson M, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol 2010;118:434–40.
[52] Lee CJ, Scheiman J, Anderson MA, Hines OJ, Reber HA, Farrell J, et al. Risk of malignancy in resected cystic tumors of the pancreas < or =3 cm in size: is it safe to observe asymptomatic patients? A multi-institutional report. J Gastrointest Surg 2008;12:234–42.
[53] Park WG, Mascarenhas R, Palaez-Luna M, Smyrk TC, O'Kane D, Clain JE, et al. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. Pancreas 2011;40:42–5.
[54] Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology 2004;126:1330–6.
[55] Cizginer S, Turner B, Bilge AR, Karaca C, Pitman MB, Brugge WR. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas 2011;40:1024–8.
[56] Genevay M, Mino-Kenudson M, Yaeger K, Ioannis T, Konstantinidis IT, Ferrone CR, et al. Cytology adds value to imaging studies for risk assessment of malignancy in pancreatic mucinous cysts. Ann Surg 2011;254:977–83.
[57] Sainani NI, Saokar A, Deshpande V, Fernandez-del Castillo C, Hahn P, Sahani DV. Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. Am J Roentgenol 2009;193:722–31.
[58] Nakagawa A, Yamaguchi T, Ohtsuka M, Ishihara T, Sudo K, Nakamura K, et al. Usefulness of multidetector computed tomography for detecting protruding lesions in intraductal papillary mucinous neoplasm of the pancreas in comparison with single-detector computed tomography and endoscopic ultrasonography. Pancreas 2009;38:131–6.
[59] Wu J, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med 2011;3. 92ra66.
[60] Sahani DV, Kadavigere R, Blake M, Fernández-del Castillo C, Lauwers GY, Hahn PF. Intraductal papillary mucinous neoplasm of pancreas: multidetector row CT with 2D curved reformations–correlation with MRCP. Radiology 2006;238:560–9.
[61] Pitman MB. Cytology of the pancreas. In: Gray W, Kocjan G, editors. Diagnostic cytopathology. London: Churchill Livingstone; 2010.
[62] Correa-Gallego C, Ferrone CR, Thayer SP, Wargo JA, Warshaw AL. Fernández-del Castillo C. Incidental pancreatic cysts: do we really know what we are watching? Pancreatology 2010;10:144–50.
[63] van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc 2005;62:383–9.
[64] Frossard JL, Amouyal P, Amouyal G, Palazzo L, Amaris J, Soldan M, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol 2003;98:1516–24.
[65] Belsley NA, Pitman MB, Lauwers GY, Brugge WR, Deshpande V. Serous cystadenoma of the pancreas: limitations and pitfalls of endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 2008;114:102–10.
[66] Recine M, Kaw M, Evans DB, Krishnamurthy S. Fine-needle aspiration cytology of mucinous tumors of the pancreas. Cancer 2004;102:92–9.
[67] Michaels PJ, Brachtel EF, Bounds BC, Brugge WR, Pitman MB. Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. Cancer 2006;108:163–73.
[68] Layfield LJ, Cramer H. Fine-needle aspiration cytology of intraductal papillary-mucinous tumors: a retrospective analysis. Diagn Cytopathol 2005; 32:16–20.
[69] Emerson RE, Randolph ML, Cramer HM. Endoscopic ultrasound-guided fine-needle aspiration cytology diagnosis of intraductal papillary mucinous neoplasm of the pancreas is highly predictive of pancreatic neoplasia. Diagn Cytopathol 2006;34:457–62.
[70] Maire F, Couvelard A, Hammel P, Ponsot P, Palazzo L, Aubert A, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc 2003;58: 701–6.
[71] Maire F, Voitot H, Aubert A, Palazzo L, O'Toole D, Couvelard A, et al. Intraductal papillary mucinous neoplasms of the pancreas: performance of pancreatic fluid analysis for positive diagnosis and the prediction of malignancy. Am J Gastroenterol 2008;103:2871–7.
[72] Pitman MB, Michaels PJ, Deshpande V, Brugge WR, Bounds BC. Cytological and cyst fluid analysis of small (≤3 cm) branch duct intraductal papillary mucinous neoplasms adds value to patient management decisions. Pancreatology 2008;8:277–84.
[73] Wiesenauer CA, Schmidt CM, Cummings OW, Yiannoutsos CT, Howard TJ, Wiebke EA, et al. Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. Arch Surg 2003;138:610–7. discussion 617–618.
[74] Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukushima N, et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan Pancreas Society. Pancreas 2011;40:67–71.
[75] Hirooka Y, Goto H, Itoh A, Hashimoto S, Niwa K, Ishikawa H, et al. Case of intraductal papillary mucinous tumor in which endosonography-guided fine-needle aspiration biopsy caused dissemination. J Gastroenterol Hepatol 2003;18:1323–7.
[76] Yamaguchi K, Nakamura M, Shirahane K, Kawamoto M, Konomi H, Ohta M, et al. Pancreatic juice cytology in IPMN of the pancreas. Pancreatology 2005; 5:416–21. discussion 421.
[77] Hirono S, Tani M, Kawai M, Okada K, Miyazawa M, Shimizu A, et al. The carcinoembryonic antigen level in the pancreatic juice and mural nodule size are predictors of malignancy for branch duct type intraductal papillary mucinous neoplasms of the pancreas. Ann Surg in press.
[78] Procacci C, Graziani R, Bicego E, Bergamo-Andreis IA, Guarise A, Valdo M, et al. Serous cystadenoma of the pancreas: report of 30 cases with emphasis on the imaging findings. J Comput Assist Tomogr 1997;21:373–82.
[79] Choi JY, Kim MJ, Lee JY, Lim JS, Chung JJ, Kim KW, et al. Typical and atypical manifestations of serous cystadenoma of the pancreas: imaging findings with pathological correlation. Am J Roentgenol 2009;193:136–42.
[80] Goh BKP, Tan YM, Yap WM, Cheow PC, Chow PK, Chung YF, et al. Pancreatic serous oligocystic adenomas: clinicopathological features and a comparison with serous microcystic and mucinous cystic neoplasms. World J Surg 2006; 30:1553–9.
[81] Kim SY, Lee JM, Kim SH, Shin KS, Kim YJ, An SK, et al. Macrocystic neoplasms of the pancreas: CT differentiation of serous oligocystic adenoma from mucinous cystadenoma and intraductal papillary mucinous tumor. Am J Roentgenol 2006;187:1192–8.
[82] Cohen-Scali F, Vilgrain V, Brancatelli G, Hammel P, Vullierme MP, Sauvanet A, et al. Discrimination of unilocular macrocystic serous cystadenoma from pancreatic pseudocyst and mucinous cystadenoma with CT: initial observations. Radiology 2003;228:727–33.
[83] Couvelard A, Sauvanet A, Kianmanesh R, Hammel P, Colnot N, Levy 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;242:778–80. discussion, 774-778.
[84] Jang JY, Kim SW, Ahn YJ, Yoon YS, Choi MG, Lee KU, et al. Multicenter analysis of clinicopathologic features of intraductal papillary mucinous tumor of the pancreas: is it possible to predict the malignancy before surgery? Ann Surg Oncol 2005;12:124–32.
[85] 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;204:987–93.
[86] 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.
[87] Farnell MB. Surgical management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. J Gastrointest Surg 2008;12:414–6.
[88] Crippa S, Tamburrino D, Partelli S, Salvia R, Germenia S, Bassi C, et al. Total pancreatectomy: indications, different timing, and perioperative and long-term outcomes. Surgery 2011;149:79–86.
[89] Stauffer JA, Nguyen JH, Heckman MG, Grewal MS, Dougherty M, Gill KR, et al. Patient outcomes after total pancreatectomy: a single centre contemporary experience. HPB (Oxford) 2009;11:483–92.
[90] Cheon YK, Cho YD, Jeon SR, Moon JH, Jeong SW, Hur KY, et al. Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. Am J Gastroenterol 2010;105:1963–9.
[91] Eguchi H, Ishikawa O, Ohigashi H, Sasaki Y, Yamada T, Nakaizumi A, et al. Role of intraoperative cytology combined with histology in detecting continuous and skip type intraductal cancer existence for intraductal papillary mucinous carcinoma of the pancreas. Cancer 2006;107:2567–75.
[92] Kang MJ, Jang JY, Kim SJ, Lee KB, Ryu JK, Kim YT, et al. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. Clin Gastroenterol Hepatol 2011;9:87–93.
[93] 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.
[94] Nagai K, Doi R, Ito T, Koizumi M, Masui T, Kawaguchi Y, 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.
[95] Sai JK, Suyama M, Kubokawa Y, Watanabe S, Maehara T. Pancreatic-duct-lavage cytology in candidates for surgical resection of branch-duct intraductal papillary mucinous neoplasm of the pancreas: should the international consensus guidelines be revised? Gastrointest Endosc 2009;69: 434–40.
[96] Rautou PE, Levy 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.
[97] Weinberg BM, Spiegel BM, Tomlinson JS, Farrell JJ. Asymptomatic pancreatic cystic neoplasms: maximizing survival and quality of life using Markov-based clinical nomograms. Gastroenterology 2010;138:531–40.

[98] Crippa S, Salvia R, Warshaw AL, Dominguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg 2008;247:571–9.
[99] 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.
[100] Sarr MG, Carpenter HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, et al. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms? Ann Surg 2000;231:205–12.
[101] Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: indications and outcomes in 235 patients. Ann Surg 1999; 229:693–8.
[102] Kooby DA, Gillespie T, Bentrem D, Nakeeb A, Schmidt MC, Merchant NB, et al. Left-sided pancreatectomy: a multicenter comparison of laparoscopic and open approaches. Ann Surg 2008;248:438–46.
[103] Rodriguez JR, Madanat MG, Healy BC, Thayer SP, Warshaw AL, Fernández CC. Distal pancreatectomy with splenic preservation revisited. Surgery 2007; 141:619–25.
[104] Kobayashi G, Fujita N, Noda Y, Kimura K, Yago A, Yamazaki T, et al. Histological features and prognosis of mucinous cystic tumors of the pancreas. In: Wakui A, Yamauchi H, Ouchi K, editors. Carcinoma of the pancreas and biliary tract. Tohoku University Press; 1999. p. 213–8.
[105] 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.
[106] Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann Surg 1998;228: 685–91.
[107] Blanc B, Sauvanet A, Couvelard A, Pessaux P, Dokmak S, Vullierme MP, et al. Limited pancreatic resections for intraductal papillary mucinous neoplasm. J Chir (Paris) 2008;145:568–78 [in French with English abstract].
[108] Falconi M, Mantovani W, Crippa S, Mascetta G, Salvia R, Pederzoli P. Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008;95:85–91.
[109] Crippa S, Partelli S, Falconi M. Extent of surgical resections for intraductal papillary mucinous neoplasms. World J Gastrointest Surg 2010;2:347–51.
[110] Takeyoshi I, Ohwada S, Nakamura S, Ogawa T, Kawashima Y, Ikeya T, et al. Segmental pancreatectomy for mucin-producing pancreatic tumors. Hepatogastroenterology 1999;46:2585–8.
[111] Warshaw AL, Rattner DW, Fernández CC, Z'Graggen K. Middle segment pancreatectomy: a novel technique for conserving pancreatic tissue. Arch Surg 1998;133:327–31.
[112] Sperti C, Pasquali C, Ferronato A, Pedrazzoli S. Median pancreatectomy for tumors of the neck and body of the pancreas. J Am Coll Surg 2000;190:711–6.
[113] Shimada K, Sakamoto Y, Esaki M, Kosuge T, Hiraoka N. Role of medial pancreatectomy in the management of intraductal papillary mucinous neoplasms and islet cell tumors of the pancreatic neck and body. Dig Surg 2008;25:46–51.
[114] 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.
[115] Adham M, Giunippero A, Hervieu V, Courbiere M, Partensky C. Central pancreatectomy: single-center experience of 50 cases. Arch Surg 2008;143: 175–80. discussion 80–81.
[116] Kimura W, Fuse A, Hirai I, Suto K. Spleen-preserving distal pancreatectomy for intraductal papillary-mucinous tumor (IPMT). Hepatogastroenterology 2004;51:86–90.
[117] Talamini MA, Moesinger R, Yeo CJ, Poulose B, Hruban RH, Cameron JL, et al. Cystadenomas of the pancreas: is enucleation an adequate operation? Ann Surg 1998;227:896–903.
[118] Madura JA, Yum MN, Lehman GA, Sherman S, Schmidt CM. Mucin secreting cystic lesions of the pancreas: treatment by enucleation. Am Surg 2004;70: 106–12.
[119] Sciaudone G, Perniceni T, Levy P, Bougaran J, Gayet B. Enucleation of intraductal papillary-mucinous tumor of the head of the pancreas. Report of 2 cases. Gastroenterol Clin Biol 2000;24:121–4 [in French with English abstract].
[120] Murakami Y, Uemura K, Yokoyama Y, Sasaki M, Morifuji M, Hayashidani Y, et al. Pancreatic head resection with segmental duodenectomy for intraductal papillary mucinous tumors of the pancreas. J Gastrointest Surg 2004; 8:713–9.
[121] Cho A, Arita S, Koike N, Isaka N, Kusume K, Makino H, et al. Ventral pancreatectomy associated with segmental duodenectomy including the major papilla. Hepatogastroenterology 2007;54:2392–4.
[122] Ohwada S, Ogawa T, Kasahara M, Kawate S, Koyama T, Izumi M, et al. Ventral pancreas-preserving pancreatic head and body resection. Hepatogastroenterology 2001;48:1622–4.
[123] Sharma MS, Brams DM, Birkett DH, Munson JL. Uncinatectomy: a novel surgical option for the management of intraductal papillary mucinous tumors of the pancreas. Dig Surg 2006;23:121–4.
[124] Yamaguchi K, Shimizu S, Yokohata K, Noshiro H, Chijiiwa K, Tanaka M. Ductal branch-oriented minimal pancreatectomy: two cases of successful treatment. J Hepatobiliary Pancreat Surg 1999;6:69–73.
[125] Lee SE, Jang JY, Yang SH, Kim SW. Intraductal papillary mucinous carcinoma with atypical manifestations: report of two cases. World J Gastroenterol 2007;13:1622–5.
[126] Mizuta Y, Akazawa Y, Shiozawa K, Ohara H, Ohba K, Ohnita K, et al. Pseudomyxoma peritonei accompanied by intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 2005;5:470–4.
[127] Vijan SS, Ahmed KA, Harmsen WS, Que FG, Reid-Lombardo KM, Nagorney DM, et al. Laparoscopic vs open distal pancreatectomy: a single-institution comparative study. Arch Surg 2010;145:616–21.
[128] Gumbs AA, Gres P, Madureira FA, Gayet B. Laparoscopic vs. open resection of noninvasive intraductal pancreatic mucinous neoplasms. J Gastrointest Surg 2008;12:707–12.
[129] Pryor A, Means JR, Pappas TN. Laparoscopic distal pancreatectomy with splenic preservation. Surg Endosc 2007;21:2326–30.
[130] Hawes RH. The evolution of endoscopic ultrasound: improved imaging, higher accuracy for fine needle aspiration and the reality of endoscopic ultrasound-guided interventions. Curr Opin Gastroenterol 2010;26: 436–44.
[131] Gan SI, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc 2005;61: 746–52.
[132] Oh HC, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc 2008;67:636–42.
[133] Oh HC, Seo DW, Song TJ, Moon SH, Park DH, Soo Lee S, et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterology 2011;140:172–9.
[134] DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc 2009;70:710–23.
[135] Oh HC, Seo DW, Yu E, Kim SC, Moon SH, Park do H, et al. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? Scand J Gastroenterol 2009;44:242–7.
[136] 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.
[137] Yamaguchi K, Nakamura K, Yokohata K, Shimizu S, Chijiiwa K, Tanaka M. Pancreatic cyst as a sentinel of in situ carcinoma of the pancreas. Report of two cases. Int J Pancreatol 1997;22:227–31.
[138] Sawai Y, Yamao K, Bhatia V, Chiba T, Mizuno N, Sawaki A, et al. Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms. Endoscopy 2010;42:1077–84.
[139] Shi C, Klein AP, Goggins M, Maitra A, Canto M, Ali S, et al. Increased prevalence of precursor lesions in familial pancreatic cancer patients. Clin Cancer Res 2009;15:7737–43.
[140] Poultsides GA, Reddy S, Cameron JL, Hruban RH, Pawlik TM, Ahuja N, et al. Histopathologic basis for the favorable survival after resection of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma of the pancreas. Ann Surg 2010;251:470–6.
[141] 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.
[142] 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.
[143] Adsay NV, Merati K, Andea A, Sarkar F, Hruban RH, Wilentz RE, et al. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. Mod Pathol 2002;15: 1087–95.
[144] 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.
[145] Nara S, Shimada K, Kosuge T, Kanai Y, Hiraoka N. Minimally invasive intraductal papillary-mucinous carcinoma of the pancreas: clinicopathologic study of 104 intraductal papillary-mucinous neoplasms. Am J Surg Pathol 2008;32:243–55.
[146] 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.
[147] Nakata K, Ohuchida K, Aishima S, Sadakari Y, Kayashima T, Miyasaka Y, et al. Invasive carcinoma derived from intestinal-type intraductal papillary mucinous neoplasm is associated with minimal invasion, colloid carcinoma, and less invasive behavior, leading to a better prognosis. Pancreas 2011;40:581–7.
[148] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
[149] Furukawa T, Hatori T, Fujita I, Yamamoto M, Kobayashi M, Ohike N, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut 2011;60:509–16.
[150] Luttges J, Zamboni G, Longnecker D, Kloppel 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.
[151] Furukawa T, Klöppel G, Adsay NV, 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.
[152] Sadakari Y, Ohuchida K, Nakata K, Ohtsuka T, Aishima S, Takahata S, et al. Invasive carcinoma derived from the nonintestinal type intraductal papillary mucinous neoplasm of the pancreas has a poorer prognosis than that derived from the intestinal type. Surgery 2010;147:812–7.
[153] Mino-Kenudson M, Fernández-del Castillo C, Baba Y, Valsangkar NP, Liss AS, Hsu M, et al. Prognosis of invasive IPMN depends on histological and precursor epithelial subtypes. Gut 2011;60:1712–20.
[154] Basturk O, Khayyata S, Klimstra DS, Hruban RH, Zamboni G, Coban I, et al. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. Am J Surg Pathol 2010;34:364–70.
[155] Adsay NV, Adair CF, Heffess CS, Klimstra DS. Intraductal oncocytic papillary neoplasms of the pancreas. Am J Surg Pathol 1996;20:980–94.
[156] Patel SA, Adams R, Goldstein M, Moskaluk CA. Genetic analysis of invasive carcinoma arising in intraductal oncocytic papillary neoplasm of the pancreas. Am J Surg Pathol 2002;26:1071–7.
[157] Hibi Y, Fukushima N, Tsuchida A, Sofuni A, Itoi T, Moriyasu F, et al. Pancreatic juice cytology and subclassification of intraductal papillary mucinous neoplasms of the pancreas. Pancreas 2007;34:197–204.
[158] 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.
[159] Paye F, Sauvanet A, Terris B, Ponsot P, Vilgrain V, Hammel P, et al. Intraductal papillary mucinous tumors of th pancreas: pancreatic resections guided by preoperative morphological assessment and intraoperative frozen section examination. Surgery 2000;127:536–44.
[160] 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.
[161] Basturk O, Coban I, Adsay NV. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. Arch Pathol Lab Med 2009; 133:423–38.
[162] Pour PM, Konishi Y, Kloppel G, Longnecker DS, editors. Atlas of exocrine pancreatic tumors, morphology, biology, and diagnosis with an international guide for tumor classification. Tokyo: Springer-Verlag; 1994. p. pp265–279.
[163] Yamaguchi K, Ohuchida J, Ohtsuka T, Nakano K, Tanaka M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology 2002;2:484–90.
[164] Yamaguchi K, Kanemitsu S, Hatori T, Maguchi H, Shimizu Y, Tada M, et al. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. Pancreas 2011;40:571–80.
[165] Sawhney MS, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. Gastrointest Endosc 2009;69:1106–10.
[166] Shen J, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. Cancer Cytopathol 2009;117:217–27.
[167] Toll AD, Kowalski T, Loren D, Bibbo M. The added value of molecular testing in small pancreatic cysts. JOP 2010;11:582–6.
[168] Ingkakul T, Sadakari Y, Ienaga J, Satoh N, Takahata S, Tanaka M. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. Ann Surg 2010;251:70–5.
[169] 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.
[170] Tanno S, Nakano Y, Koizumi K, Sugiyama Y, Nakamura K, Sasajima J, et al. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. Pancreas 2010;39: 36–40.
[171] Ikeuchi N, Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, et al. Prognosis of cancer with branch duct type IPMN of the pancreas. World J Gastroenterol 2010;16:1890–5.
[172] Tanno S, Nakano Y, Sugiyama Y, Nakamura K, Sasajima J, Koizumi K, et al. Incidence of synchronous and metachronous pancreatic carcinoma in 168 patients with branch duct intraductal papillary mucinous neoplasm. Pancreatology 2010;10:173–8.
[173] Ohtsuka T, Kono H, Tanabe R, Nagayoshi Y, Mori Y, Sadakari Y, et al. Follow-up study after resection of intraductal papillary mucinous neoplasm of the pancreas; special references to the multifocal lesions and development of ductal carcinoma in the remnant pancreas. Am J Surg; 2011 [Epub ahead of print].
[174] Le Borgne J, de Calan L, Partensky C. Cystadenomas and cystadenocarcinomas of the pancreas: a multiinstitutional retrospective study of 398 cases. French Surgical Association. Ann Surg 1999;230:152–61.
[175] Mabrut JY, Fernandez-Cruz L, Azagra JS, Bassi C, Delvaux G, Weerts J, et al. Laparoscopic pancreatic resection: results of a multicenter European study of 127 patients. Surgery 2005;137:597–605.
[176] Tien YW, Hu RH, Hung JS, Wang HP, Lee PH. Noninvasive pancreatic cystic neoplasms can be safely and effectively treated by limited pancreatectomy. Ann Surg Oncol 2008;15:193–8.
[177] Azar C, Van de Stadt J, Rickaert F, Deviere M, Baize M, Kloppel G, et al. Intraductal papillary mucinous tumours of the pancreas. Clinical and therapeutic issues in 32 patients. Gut 1996;39:457–64.
[178] Wada K, Kozarek RA, Traverso LW. Outcomes following resection of invasive and noninvasive intraductal papillary mucinous neoplasms of the pancreas. Am J Surg 2005;189:632–6. discussion 637.
[179] 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.
[180] Cellier C, Cuillerier E, Palazzo L, Rickaert F, Flejou JF, Napoleon B, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. Gastrointest Endosc 1998;47:42–9.
[181] 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.
[182] 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.
[183] 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.
[184] Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634–8.
[185] Amundadottier LT, Thorvaldsson S, Gudbjartsson DF, Sulem P, Kristjansson K, Arnason S, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. PLoS Med 2004; 1:e65.
[186] Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007;25:1417–22.
[187] Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2007;16:342–6.
[188] Goggins M, Schutte M, Lu J, Weinstein CL, Petersen GM, Yeo CJ, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996;56:5360–4.
[189] Gruis NA, Sandkuiji LA, van der Velden PA, Bergman W, Frants RR. CDKN2 explains part of the clinical phenotype in Dutch familial atypical multiple-mole melanoma (FAMMM) syndrome families. Melanoma Res 1995;5: 169–77.
[190] Lynch HT, Fusaro RM. Pancreatic cancer and the familial atypical multiple mole melanoma (FAMMM) syndrome. Pancreas 1991;6:127–31.
[191] Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Måsbäck A, et al. High frequency of multiple melanomas and breast and pancreas carcinomas in CDKN2A mutation-positive melanoma families. J Natl Cancer Inst 2000; 92:1260–6.
[192] Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, et al. Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 1987;316:1511–4.
[193] Yamaguchi K, Chijiiwa K, Shimizu S, Yokohata K, Morisaki T, Yonemasu H, et al. Intraductal papillary neoplasm of the pancreas: a clinical review of 13 benign and four malignant tumours. Eur J Surg 1999;165:223–9.
[194] Calculli L, Pezzilli R, Brindisi C, Morabito R, Casadei R, Zompatori M. Pancreatic and extrapancreatic lesions in patients with intraductal papillary mucinous neoplasms of the pancreas: a single-centre experience. Radiol Med 2010;115:442–52.
[195] Oh SJ, Lee SJ, Lee HY, Paik YH, Lee DK, Lee KS, et al. Extrapancreatic tumors in intraductal papillary mucinous neoplasm of the pancreas. Korean J Gastroenterol 2009;54:162–6 [in Korean with English abstract].
[196] 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.
[197] Benarroch-Gampel J, Riall TS. Extrapancreatic malignancies and intraductal papillary mucinous neoplasms of the pancreas. World J Gastrointest Surg 2010;2:363–7.
[198] Reid-Lombardo KM, Mathis KL, Wood CM, Harmsen WS, Sarr MG. Frequency of extrapancreatic neoplasms in intraductal papillary mucinous neoplasm of the pancreas: implications for management. Ann Surg 2010; 251:64–9.
[199] Lee SY, Choi DW, Jang KT, Lee KT, Choi SH, Heo JS, et al. High expression of intestinal-type mucin (MUC2) in intraductal papillary mucinous neoplasms coexisting with extrapancreatic gastrointestinal cancers. Pancreas 2006;32: 186–9.
[200] Khan S, Sclabas G, Reid-Lombardo KM. Population-based epidemiology, risk factors and screening of intraductal papillary mucinous neoplasm patients. World J Gastrointest Surg 2010;2:314–8.