Original Article

Accuracy of 2012 International Consensus Guidelines for the prediction of malignancy of branch-duct intraductal papillary mucinous neoplasms of the pancreas

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Abstract

Objective: To determine accuracy of 2012 International Consensus Guidelines (ICG) predicting malignancy in a surgical cohort of branch-duct intraductal papillary mucinous neoplasms (BD-IPMN).

Methods: This study included all consecutive patients with final pathological diagnosis of pure BD-IPMN resected between 2006 and 2014 at Beaujon Hospital. Neoplasms were classified as malignant in presence of high-grade dysplasia (HGD) or invasive carcinoma. Medical, pathological, and radiological data were retrospectively recorded.

Results: One hundred and twenty patients (65 males, mean age: 57.9 ± 10.8 years) were included. Malignant BD-IPMN accounted for 30% (HGD: 18%, invasive: 12%). Thickened cyst walls (odds ratio (OR): 3.058, 95% confidence interval (CI 95%): 1.102–8.484, $p = 0.032$), main duct diameter 5–9 mm (OR: 3.395, CI 95%: 1.349–8.543, $p = 0.007$), and mural nodule (OR: 3.802, CI 95%: 1.156–12.511, $p = 0.028$) were independently associated with malignancy in multivariate analysis. Among the 89 patients (74%) who underwent surgical resection with ICG criteria, the malignancy rate was 38%, compared with 6% in the 31 ICG-negative group. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for malignancy of having at least one ICG criteria were 94%, 34%, 38%, 94%, and 53%, respectively. Patients with malignant tumors had more ICG criteria than those with benign lesions (2.06 ± 0.98 vs. 0.99 ± 0.95, $p < 0.001$).

Conclusions: 2012 ICG criteria are useful to manage BD-IPMN permitting not to miss a malignant form (NPV of 94%), but frequently point out unnecessary surgery (PPV of 38%). Malignancy rate increases with the number of ICG criteria. In patients with only one criterion, additional criteria would be necessary.

Introduction

Intraductal papillary and mucinous neoplasms of the pancreas (IPMN) are precancerous lesions diagnosed with an increasing frequency. It is widely accepted that main duct (MD) and mixed-type should be distinguished from branch-duct (BD)-IPMN, due to different risk of malignancy.[1] All authors agree with the indication of surgical resection for MD-IPMNs because of high rates of malignancy, whereas the management of BD-IPMN is not so clear. With an overall risk of malignant transformation estimated at 6–40%, a close surveillance of BD-PMN seems reasonable except if

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predictive factors of malignancy are present or appear during follow-up.[2–7]

In order to propose a management algorithm of BD-IPMN, the International Consensus Guidelines (ICG) have been updated recently in 2012 and categorized predictors of malignancy as high-risk stigmata and worrisome features.[8] High-risk stigmata include (a) obstructive jaundice, (b) enhanced solid component, and (c) dilation of the main pancreatic duct (MD) to a diameter greater than 10 mm. Worrisome features include (a) history of pancreatitis, (b) maximal cyst diameter greater than 30 mm, (c) thickened and enhanced cyst walls, (d) MD diameter 5–9 mm, (e) non-enhanced mural nodules, (f) abrupt change in the caliber of the MD with distal pancreatic atrophy, and (g) lymphadenopathy. Since this publication, several studies have evaluated the usefulness of the ICG.[9–12] However, the interpretation of the results was not easy, due to several factors: variation in the definition of ICG-positive neoplasms among the different studies (for example, some included mixed type), non-systematic surgery, symptoms not always considered, and unclear definition of the size of mural nodules.

The aim of the present study was to determine the factors associated with malignancy in a large single center series of patients who had pancreatic resection for pure BD-IPMN and whether the association of several criteria increased the risk of malignancy. All patients had complete preoperative investigations, including computed tomography (CT) scan, magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We focused on the positive and negative predictive values of the ICG criteria to diagnose malignant BD-IPMN.

Methods

Inclusion and exclusion criteria

All consecutive patients who underwent surgical pancreatic resection at Beaujon Hospital with final diagnosis of BD-IPMN between January 2006 and March 2014 were included. Histology was assessed according to the 2010 World Health Organization criteria.[13] Dysplasia was graded according to the fourth edition of the WHO classification system and categorized as low, intermediate or high-grade dysplasia (HGD)/carcinoma *in situ* and invasive carcinoma.[14] When various degrees of dysplasia were present in the same specimen, lesions were categorized according to the most severe. Finally, both HGD and invasive carcinoma were classified as malignant neoplasms. In addition to pathological grades, IPMNs were divided into four subtypes: intestinal, gastric, pancreato-biliary, and oncocytic.[15] Patients with histological involvement of MD were excluded.

Imaging procedures

All patients included in the study had preoperatively undergone CT scan, MRI with pancreatography, and EUS. A radiologist (MPV) expert in pancreatic imaging reviewed all CT scan and MRI procedures. Expert endoscopists (AA, FM) with great experience in pancreatic diseases performed all EUS procedures.

Multiphasic helical CT was performed with different CT machines. First, a CT Twin Marconi (Halifa, Israel) was used: unenhanced phase (section thickness 5 mm) was followed by an enhanced study at the late arterial phase referred to as the pancreatic phase (section thickness 2.5 mm, pitch 1.5) and during the portal venous phase (section thickness 5 mm, pitch 1.5). Thin-slice helical triple-phase CT scan was focused on the pancreas and its surroundings. Light speed VCT 64 GE (Milwaukee) was also used with two sequential breath-hold helical acquisitions performed 45 and 70 s after initiation of intravenous infusion of iodinated contrast material.

All magnetic resonance cholangiopancreatography (MRCP) tests were performed on a single unit (Philips Intera, 1.5 T) with the followings sequences: T2 SPIR axial weighted sequence with fat saturation, T2 single shot axial and coronal planes, T1 gradient axial sequence with fat saturation, T1 weighted dynamic sequence fast breath hold axial, and T1 weighted delayed (120 s) post enhancement.

All EUS procedures were performed using a radial Olympus GFUM 20/EUM 20 (Olympus, Rungis, France) under sedation according to the standard medical care guidelines.

Clinical and morphological data

Variables including sex, age, circumstances at diagnosis (obstructive jaundice, acute pancreatitis, abdominal pain), and personal and/or family history of pancreatic cancer (defined as at least one first or second-degree relative diagnosed with pancreatic adenocarcinoma) were collected.

At imaging, the following data were recorded: cyst size, MD diameter, mural nodules (enhancing or not, size), thickened cyst walls, abrupt change in MD diameter, lymphadenopathy, and cytology if performed.

Finally, the correlation between all these features and the incidence of malignant neoplasms was investigated, in order to find out the predictive factors for malignancy. Abnormal findings were classified into two categories, i.e. "high-risk stigmata" and "worrisome features," as already defined in the ICG 2012.[8] A correlation between the number of ICG criteria and the risk of malignancy was searched for.

Statistical analysis

Categorical variables were compared using χ^2 test or Fischer's exact test when necessary. Normally distributed continuous variables were analyzed by Student t test and non-normally distributed variables by the Mann–Whitney U-test. All continuous data are presented as mean ± standard error of the mean and the optimal cutoff levels to differentiate malignant tumors were determined by receiver operating characteristic (ROC) curves identifying the point which showed equal sensitivity and specificity on the curve. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for malignancy were calculated for each feature. A multidimensional analysis was performed using a logistic regression analysis. The stepwise selection option was used *p*-values below 0.20 were considered as significant as level of entry in the model. Statistical significance was achieved when *p*-value < 0.05 in univariate and multivariate analysis. Statistical analysis was performed using SPSS version 21 (IBM, Bois-Colombes, France).

Results

Patient characteristics

One hundred and thirty consecutive patients with pathological criteria of BD-IPMN were included. Among them, 10 were subsequently excluded: two patients underwent surgery for pancreatic serous cystadenoma in whom a BD-IPMN was incidentally found in the specimen and eight patients had a histological involvement of MD in the pathological specimen. Finally, 120 patients with strictly defined BD-IPMN were included in the study. There were 65 men and mean age was 57.9 ± 10.8 years.

Diagnosis was made as follows: pancreatic pain ($n = 18$, 15%), acute pancreatitis ($n = 53$, 44% – the average number of pancreatitis prior to surgery was 2.3 ± 1.7 (range 1–10), jaundice ($n = 5$, 4%), diarrhea ($n = 1$, 1%), incidental ($n = 26$, 22%), and follow-up of patients with family history of pancreatic cancer ($n = 17$, 14%). All 120 patients were preoperatively evaluated by CT, MRI, and EUS.

The indication for surgery was at least one ICG criteria in 89 pts (74%), symptoms in 26 pts (22%). In 5 pts (4%), we considered surgical resection in presence of cyst between 20 and 30 mm and family history of pancreatic cancer.

Pancreatic resections were as follows: Whipple procedure ($n = 55$, 46%); enucleation ($n = 33$, 27%); left pancreatectomy ($n = 23$, 20%); central pancreatectomy ($n = 9$, 7%).

Histopathological characteristics

Among the 120 patients operated on for BD-IPNM, 30 patients (25%) had low-grade dysplasia (LGD), 54 (45%) had medium-grade dysplasia (MGD), 22 (18%) had HGD, and the remaining 14 (12%) had an invasive carcinoma. Malignant BD-IPMN accounted for 30%. Within the 14 invasive carcinomas, four had lymph node involvement.

The IPMN phenotype was as follows: 7 (6%) pancreatobiliary, 33 (28%) intestinal, 68 (57%) gastric, and 12 (10%) mixed type combining intestinal and gastric phenotypes. None had an oncocytic phenotype. In LGD IPMN, gastric phenotype was the most common (90%).

Factors predicting malignancy

The diagnostic value of the clinicopathological features for malignancy is shown in Table 1. Male gender and obstructive jaundice were associated with malignancy ($p = 0.028$ and 0.002, respectively). The occurrence of acute pancreatitis and family history of pancreatic cancer were not associated with malignancy.

The mean diameter of the cyst was 22.4 ± 11.4 mm. There was no difference in mean cyst size between benign and malignant tumors (21.2 vs. 25.4 mm, respectively, $p = 0.060$). Considering patients with cysts between 5–9 mm, 10–19 mm, 20–29 mm, 30–39 mm, and ≥40 mm, no statistically significant differences for malignancy were observed in the subgroup analysis ($p = 0.270$). Cyst size greater than 30 mm was the only feature considered for surgery in 6 asymptomatic patients with no other worrisome features or high-risk stigmata. The median cyst size in these patients was 36.8 mm (range 30–47 mm) and only one of them had malignant IPMN (HGD).

Mean MD size was 4.6 ± 2.7 mm with a statistical difference between patients with or without malignancy (5.6 mm vs. 4.2 mm respectively, $p = 0.01$) in BD. Optimal cutoff point for malignancy was set at 5 mm by ROC analysis ($p = 0.001$), with a sensitivity of 64% and a specificity of 68% (AUC 0.67).

Thickened cyst walls were observed in 27 patients (22%) with a PPV of 48%.

A mural nodule was present in 17 patients (14%) on CT, MRI, or EUS. The median size of mural nodule was 10 mm (range 2–19 mm) by CT or MRI and 5 mm (range 3–16 mm) by EUS. The presence of any mural nodule was significantly associated with malignancy (PPV of 59%, $p = 0.005$). Nine patients (7%) had enhancing mural nodule, median size 10 mm (range 2–19 mm), with a PPV of 78% ($p < 0.05$). MGD, HGD, or invasive cancer was found in 2, 3,

Table 1. Univariate analysis of predictive factors of malignancy in BD-IPMN.

Imaging findings	n (%)	Malignant tumors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p
Clinical characteristics								
Male gender	65 (54%)	25 (8 Inv)	69%	52%	38%	80%	48%	**0.028**
Obstructive jaundice	5 (4%)	5 (4 Inv)	14%	100%	100%	73%	74%	**0.002**
Pancreatitis	53 (44%)	14 (4 Inv)	39%	54%	26%	67%	49%	0.446
All symptomatic patients	71(59%)	19 (6 Inv)	53%	34%	26%	63%	40%	0.190
Age >60	60 (50%)	20 (8 Inv)	56%	52%	33%	73%	53%	0.426
Family history of pancreatic cancer	17 (14%)	4 (2 Inv)	11%	84%	23%	69%	62%	0.530
Imaging findings								
MD ≥10 mm	6 (5%)	4 (0 Inv)	11%	98%	67%	72%	72%	0.065
MD size 5–9 mm	44 (37%)	19 (9 Inv)	59%	70%	43%	82%	38%	**0.004**
MD ≥5 mm	50 (42%)	23 (9 Inv)	64%	68%	46%	81%	67%	**0.001**
Cyst ≥30 mm	43 (36%)	16 (8 Inv)	44%	68%	37%	74%	61%	0.198
Thickened walls	27 (22%)	13 (8 Inv)	36%	83%	48%	75%	69%	**0.019**
Mural nodule (enhancing or not)	17 (14%)	10 (5 Inv)	28%	92%	59%	75%	72%	**0.005**
Abrupt change in caliber of MD	14 (12%)	7 (3 Inv)	19%	92%	50%	73%	70%	0.118

BD-IPMN: branch-duct intraductal papillary neoplasms; PPV: positive predictive value; NPV: negative predictive value; MD: main pancreatic duct; Inv: invasive carcinoma

and 4 patients, respectively. Among patients with non-enhancing mural nodules, final histopathological diagnosis was LGD, MGD, HGD, or invasive cancer in 1, 4, 2, and 1 patients, respectively.

Four patients had a parenchyma infiltrating tissular lesion on MRI and CT: all of them had invasive carcinoma on histological specimen ($p = 0.017$).

No patient had lymphadenopathy.

At univariate analysis (Table 1), mural nodule ($p = 0.05$), thickened walls ($p = 0.019$) and the MD diameter from 5–9 mm ($p = 0.004$) were significantly associated with malignancy.

At multivariate analysis (Table 2), mural nodule (odds ratio (OR): 3.802, 95% confidence interval (CI 95%): 1.156–12.511, $p = 0.028$), MD diameter from 5–9 mm (OR: 3.395, CI 95%: 1.349–8.543, $p = 0.007$), and thickened cyst walls (OR: 3.058, CI 95%: 1.102–8.484, $p = 0.032$) were confirmed to be independently associated with malignancy.

Value of 2012 ICG criteria

In the present series, 89 patients (74%) underwent surgical resection according to 2012 ICG criteria. The malignancy rate was 38% (34/89), compared with 6% (2/31) in the ICG-negative group (Table 3). These two ICG-negative patients underwent surgery for relief of symptoms; they had 20 and 11 mm cystic lesions and HGD at final pathological analysis. The sensitivity, specificity, PPV, NPV, and accuracy for malignancy of at least one ICG criteria were 94%, 34%, 38%, 94%, and

Table 2. Multivariate analysis of potential predictive factors for malignancy in BD-IPMN.

	Odds ratio	95% CI	p-value
Male gender	2.308	0.888–5.999	0.086
Cyst ≥30 mm	1.224	0.461–3.246	0.685
Thickened walls	3.058	1.102–8.484	**0.032**
MD size 5–9 mm	3.395	1.349–8.543	**0.009**
Mural nodule	3.802	1.156–12.511	**0.028**

BD-IPMN: branch-duct intraductal papillary neoplasms; CI: confidence interval; MD: main pancreatic duct

53%, respectively. Patients with malignant neoplasms had significantly more ICG criteria than those with benign tumors (2.06 ± 0.98 vs. 0.99 ± 0.95, respectively, $p < 0.001$). PPV increased from 15% to 56% in patients with two criteria instead of one (Table 4).

Discussion

The present study has reported a large monocentric series of strictly defined BD-IPMN on histological examination in order to characterize the risk factors for malignancy, to evaluate the relevance of 2012 ICG criteria and to assess the importance of the number of criteria. The objectives of guidelines are to obtain both an excellent NPV in order not to miss a malignant BD-IPMN and an excellent PPV to avoid unnecessary surgery. The overall malignancy rate of BD-IPMN was 30% in the present study, as usually

Table 3. Value of 2012 International Consensus Guidelines criteria for prediction of malignancy.

	n (%)	Malignant tumors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p
High-risk stigmata								
Obstructive jaundice	5 (4%)	5 (4 Inv)	14%	100%	100%	73%	74%	**0.002**
MD ≥10 mm	6 (5%)	4 (0 Inv)	11%	98%	67%	72%	72%	0.065
Enhancing solid component within cyst	9 (7%)	7 (4 Inv)	19%	97%	78%	74%	78%	**0.001**
Worrisome features								
Cyst ≥30 mm	43 (36%)	16 (8 Inv)	44%	68%	37%	74%	61%	0.198
MD size 5–9 mm	44 (37%)	19 (9 Inv)	59%	70%	43%	82%	38%	**0.004**
Thickened cyst walls	27 (22%)	13 (8 Inv)	36%	83%	48%	75%	69%	**0.019**
Non-enhancing mural nodule	8 (7%)	3 (1 Inv)	8%	94%	37%	70%	37%	0.632
Abrupt change in caliber of MPD	14 (12%)	7 (3 Inv)	19%	92%	50%	73%	70%	0.118

PPV: positive predictive value; NPV: negative predictive value; MD: main pancreatic duct; Inv: invasive carcinoma

Table 4. Diagnostic value based on the number of factors predicting malignancy.

Number of factors	n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1	40 (33%)	75	46	15	93	49
2	36 (30%)	91	64	56	82	73
3	7 (6%)	67	91	57	74	87
≥4	6 (5%)	67	93	67	72	89
≥1	89 (74%)	94	34	38	94	53

PPV: positive predictive value; NPV: negative predictive value.

reported in the literature.[8,9,16] Among the 89 patients who underwent surgical resection according to ICG criteria, the malignancy rate was 38%, compared with 6% in the ICG-negative group. Our results demonstrate that using ICG criteria to manage BP-IPMN permits not to miss a malignant form (NPV of 94%), but frequently points out unnecessary surgery (PPV of 38%).

Within the 120 patients included, the presence of obstructive jaundice was the best criteria for malignancy (PPV of 100%) confirming its value as "high-risk stigmata." The occurrence of pancreatitis (44%) was higher than in most of the other studies,[17] probably because we included only pure BD-IPMN patients. However, as previously reported by Pelletier et al.,[18] there was no significant difference in the grade of dysplasia between pancreatitis and non-pancreatitis groups. Family history of pancreatic cancer is not part of ICG criteria.[8,19] In our series, 23% of patients with family history of pancreatic cancer had malignant BD-IPMN, half of them invasive. However, no

ICG-negative patient with family history of pancreatic cancer had a malignant tumor.

Considering the MD dilatation as an indicator of malignancy rather than a criterion to classify the IPMN in BD vs. mixed/MD-IPMN, the PPV of MD larger than 5 mm was 46%, meaning that, in nearly half of patients, passive dilation of MD associated with BD-IPMN accounted for malignant BD-IPMN. To our knowledge, the association between passive MD dilation and malignancy of BD-IPN is reported here for the first time. The abrupt change in the MD caliber had a good specificity for malignancy, but due to its very low sensitivity, this criterion was not relevant for usual practice.

We confirmed the high prognostic value of a mural nodule, significantly associated with malignancy at multivariate analysis (RR 3.802, CI 95%: 1.156–12.511). Particularly, mural nodules enhancing on MRI had excellent NPV and PPV (74% and 78%, respectively). The 2012 ICG did not mention the size of mural nodules. Kim et al. recently proposed a cutoff of 5 mm on EUS for discriminating benign and malignant

BP-IPMN with a sensitivity of 84% and a specificity of 78%.[7] The low number of patients with enhancing nodules in our series did not permit to assess a threshold for size.

Cyst size has been the most controversial criteria for predicting BD malignancy in the literature.[17] A recent meta-analysis of 5788 patients suggested that cyst size was associated with the highest OR of 62, whereas mural nodule and main duct involvement generated ORs of 9 and 7, respectively.[20] In the present study, 36% of patients had cyst size greater than 30 mm and a malignant IPMN was found in 37% of them. But among patients who underwent surgery for this sole criterion, only one patient had a malignant form. Thus, as suggested by other authors, we consider that resection of BD-IPMN based on cyst size alone is not appropriate.[10]

In 2014, Goh et al. performed a systematic review of the literature to determine the utility of Sendai criteria,[12] as initially defined in 2006. They pooled nine studies with 690 surgically resected BD-IPMN and concluded that malignancy rate was 30% in Sendai-positive and 10% in Sendai-negative patients.[12] The 2012 ICG criteria differ from 2006 by decreasing threshold for a dilated MD to 5 mm and classifying the cyst size greater than 30 mm as only a worrisome feature. More recently, some studies evaluated the ICG 2012, but there were some variations in the definition of ICG positive tumors among the different studies. A series by Ohtsuka et al. concluded that an increase in the number of predictive factors increased the sensitivity for predicting malignant potential of BD-IPMN.[21] Roch et al. hypothesized that the type (clinical versus radiological) and quantity of the 2012 ICG criteria (WFs and HRS) are of unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.[11] Patients in the HRS group had higher rates of malignant IPMN than those in the WFs group (56.5% versus 26.5%, $p = 0.0001$). There was no stepwise increase in rates of malignant or invasive IPMN with the number of WFs. A recent study published by Aso et al. in 2014 reported that the likelihood of malignant BD-IPMN increased in accordance with the number of high-risk stigmata,[9] whereas the number of WF was not significantly correlated with malignancy. In our study, patients with only one predictive factor according to ICG guidelines had a malignancy rate of 15%. PPV increased significantly to 56% for two factors. Thus, our results underline that only one predictive feature may not be enough to recommend surgical decisions and guidelines should potentially be optimized by the inclusion of additional criteria: age, comorbidities, family history of pancreatic cancer, serum tumor markers (Ca 19.9 as proposed by Jang et al.),[10] and may be new markers in cyst fluid.

The strength of the present study is that all patients underwent surgery for a final pathological diagnosis of pure BD-IPMN in a single-center. But, as in previous surgical series, the true incidence of malignancy might have been overestimated.

In conclusion, our results suggest that 2012 ICG criteria are useful to manage BP-IPMN permitting not to miss a malignant form, but frequently point out unnecessary surgery. Hence, it is necessary to consider all potential predictive factors, to look for new markers (genomic or proteomic analysis of cyst fluid, confocal EUS) but also to take care of comorbidities/surgical risk and to assess the risk of IPMN-related death in a cohort of conservatively surveyed patients with BD-IPMN and worrisome features.

Conflict of interest

None declared.

References

1. Lévy P, Jouannaud V, O'Toole D, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. *Clin Gastroenterol Hepatol* 2006; 4: 460–468.
2. Correa-Gallego C, Ferrone CR, Thayer SP, et al. Incidental pancreatic cysts: do we really know what we are watching? *Pancreatology* 2010; 10: 144–150.
3. Khannoussi W, Vullierme MP, Rebours V, et al. The long term risk of malignancy in patients with branch duct intraductal papillary mucinous neoplasms of the pancreas. *Pancreatology* 2012; 12: 198–202.
4. Kobayashi G, Fujita N, Maguchi H, et al. Natural history of branch duct intraductal papillary mucinous neoplasm with mural nodules: a Japan pancreas society multicenter study. *Pancreas* 2014; 43: 532–538.
5. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 2006; 6: 17–32.
6. Uehara H, Ishikawa O, Katayama K, et al. Size of mural nodule as an indicator of surgery for branch duct intraductal papillary mucinous neoplasm of the pancreas during follow-up. *J Gastroenterol* 2011; 46: 657–663.
7. Kim KW, Park SH, Pyo J, et al. Imaging features to distinguish malignant and benign branch-duct type intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. *Ann Surg* 2014; 259: 72–81.
8. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; 12: 183–197.

9. Aso T, Ohtsuka T, Matsunaga T, et al. "High-risk stigmata" of the 2012 international consensus guidelines correlate with the malignant grade of branch duct intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2014; 43: 1239–1243.

10. Jang JY, Park T, Lee S, et al. Validation of international consensus guidelines for the resection of branch duct-type intraductal papillary mucinous neoplasms. *Br J Surg* 2014; 101: 686–692.

11. Roch AM, Ceppa EP, DeWitt JM, et al. International Consensus Guidelines parameters for the prediction of malignancy in intraductal papillary mucinous neoplasm are not properly weighted and are not cumulative. *HPB* 2014; 16: 929–935.

12. Goh BK, Tan DM, Ho MM, et al. Utility of the Sendai consensus guidelines for branch-duct intraductal papillary mucinous neoplasms: a systematic review. *J Gastrointest Surg* 2014; 18: 1350–1357.

13. Adsay NV, Fukushima N, Furukawa T, et al. Intraductal neoplasms of the pancreas. In: Bosman T, Carneiro F, Hruban RH, et al. (eds) *WHO classification of tumours of the digestive system.* Lyon: IARC Press, 2010, pp. 304–313.

14. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2004; 28: 977–987.

15. Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch* 2005; 447: 794–799.

16. Kim TH, Song TJ, Hwang JH, et al. Predictors of malignancy in pure branch duct type intraductal papillary mucinous neoplasm of the pancreas: a nationwide multicenter study. *Pancreatology* 2015; 15: 405–410.

17. Sahora K, Mino-Kenudson M, Brugge W, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg* 2013; 258: 466–475.

18. Pelletier AL, Hammel P, Rebours V, et al. Acute pancreatitis in patients operated on for intraductal papillary mucinous neoplasms of the pancreas: frequency, severity, and clinicopathologic correlations. *Pancreas* 2010; 39: 658–661.

19. Nehra D, Oyarvide VM, Mino-Kenudson M, et al. Intraductal papillary mucinous neoplasms: does a family history of pancreatic cancer matter? *Pancreatology* 2012; 12: 358–363.

20. Anand N, Sampath K and Wu BU. Cyst features and risk of malignancy in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; 11: 913–921.

21. Ohtsuka T, Kono H, Nagayoshi Y, et al. An increase in the number of predictive factors augments the likelihood of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas. *Surgery* 2012; 151: 76–83.