Management of branch-duct intraductal papillary mucinous neoplasms: a large single-center study to assess predictors of malignancy and long-term outcomes CME

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Background and Aims: Management of branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) remains challenging. We determined factors associated with malignancy in BD-IPMNs and long-term outcomes.

Methods: This retrospective cohort study included all patients with established BD-IPMNs by the International Consensus Guidelines (ICG) 2012 and/or pathologically confirmed BD-IPMNs in a tertiary care referral center between 2001 and 2013. Main outcome measures were the association between high-risk stigmata (HRS)/worrisome features (WFs) of the ICG 2012 and malignant BD-IPMNs, performance characteristics of EUS-FNA for the diagnosis of malignant BD-IPMNs, and recurrence and long-term outcomes of BD-IPMN patients undergoing surgery or imaging surveillance.

Results: Of 364 BD-IPMN patients, 229 underwent imaging surveillance and 135 underwent surgery. Among the 135 resected BD-IPMNs, HRS/WFs on CT/magnetic resonance imaging (MRI) were similar between the benign and malignant groups, but main pancreatic duct (MPD) dilation (5-9 mm) was more frequently identified in malignant lesions. On EUS-FNA, mural nodules, MPD features suspicious for involvement, and suspicious/positive malignant cytology were more frequently detected in the malignant group with a sensitivity, specificity, and accuracy of 33%, 94%, and 86%; 42%, 91%, and 83%; and 33% 91%, and 82%, respectively. Mural nodules identified by EUS were missed by CT/MRI in 28% in the malignant group. Patients with malignant lesions had a higher risk of any IPMN recurrence during a mean follow-up period of 131 months ($P = .01$).

Conclusions: Among HRS and WFs of the ICG 2012, an MPD size of 5 to 9 mm on CT/MRI was associated with malignant BD-IPMNs. EUS features including mural nodules, MPD features suspicious for involvement, and suspicious/malignant cytology were accurate and highly specific for malignant BD-IPMNs. Our study highlights the incremental value of EUS-FNA over imaging in identifying malignant BD-IPMNs, particularly in patients without WFs and those with smaller cysts. Benign IPMN recurrence was observed in some patients up to 8 years after resection. (Gastrointest Endosc 2016;84:436-45.)

(footnotes appear on last page of article)

Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) are the most common variant of IPMNs and are most often diagnosed incidentally.[1-3] Based on the International Consensus Guidelines (ICG) 2012 for the management of BD-IPMNs, the indications for surgical resection rely on high-risk stigmata (HRS) and worrisome features (WFs) on CT and magnetic resonance imaging (MRI).[3] Increasingly, EUS-FNA has been used for the characterization of BD-IPMNs, but its overall impact on the management of this disease remains unclear. Other imaging modalities like CT and MRI remain the first-line investigation in most patients, with an expanding body of literature backing this practice.[4-10]

It has been suggested that EUS is the most reliable tool for the characterization of IPMNs.[11] The ICG 2012 recommends possible EUS-FNA for evaluation of small BD-IPMNs without WFs only in centers with expertise in EUS-FNA and cytologic interpretation.[3] Recently, based on variable strength evidence, the American Gastroenterological Association Institute (AGA) released new guidelines on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. The guidelines

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suggest that pancreatic cysts with at least 2 high-risk features, such as size $\geq$ 3 cm, a dilated main pancreatic duct (MPD), or the presence of an associated solid component, should be examined with EUS-FNA, whereas patients with pancreatic cysts < 3 cm without a solid component or a dilated pancreatic duct should undergo MRI for surveillance.[12] Overall, all current guidelines derive many of their recommendations from lower-level evidence from a limited number of studies.[13-15] Because of this and the lack of consistency across the current guidelines, the utility of EUS in the management of BD-IPMNs remains controversial compared with other imaging modalities. Although several studies have demonstrated variable associations between imaging features and malignancy in BD-IPMNs, the literature remains limited by small-size series and the heterogeneity of the imaging modalities used including cross-sectional (CT/MRI) and/or endosonographic imaging studies.

The primary objectives of our study were to evaluate the association between image-defined HRS and WFs from ICG 2012 and malignant BD-IPMNs and to determine performance characteristics of preoperative EUS-FNA in identifying malignant BD-IPMNs. The secondary objectives were to measure recurrence rates of BD-IPMNs after resection during long-term follow-up and to assess long-term outcomes in BD-IPMN patients undergoing imaging surveillance.

METHODS

Study population

This is a retrospective cohort study. Using our prospectively maintained EUS, cytology, and surgical databases, we identified patients with a confirmed diagnosis of a BD-IPMN at Indiana University Hospital between January 2001 and December 2013 (excluding an additional year of follow-up). The diagnosis of BD-IPMNs was established based on the ICG 2012 guidelines and/or pathologically confirmed pure BD-IPMNs with no MPD involvement.[3] This inclusion of patients managed operatively with MPD dilatation without MPD disease on pathology is consistent with ICG 2012 where MPD dilation (>5 mm) is considered a predictive factor for malignancy in BD-IPMNs in the absence of a main duct component.

The following lesion characteristics on CT/MRI and EUS were reviewed: cyst size (maximal diameter on CT/MRI and EUS at time of diagnosis), location, MPD diameter (maximal diameter on CT/MRI and EUS at time of diagnosis), and cyst morphology (presence of solid component, septations, and calcifications; cyst wall thickness/enhancement; mural nodules; and regional lymph node involvement). Cyst fluid analysis was recorded when available.

Patient clinical course was reviewed after surgery, if performed, and clinical/imaging follow-up if not. Using surgical pathology we classified lesions as benign (including low- or moderate-grade dysplasia) and malignant (high-grade dysplasia or invasive cancer) based on the World Health Organization classification.[16] For the purpose of study analysis, individual risks of malignancy were reclassified based on the ICG 2012 including HRS, WF, or non-WF patients. For patients with complete resection (negative margin, no tumor cells seen microscopically), recurrence was determined if new cystic lesions were detected in the remnant pancreas on CT/MRI and EUS and was strongly suspected based on fluid analysis and/or on surgical pathology if re-resection took place at any time during follow-up.

Residual tumors were defined as patients who had positive surgical margins after resection or patients with multifocal BD-IPMNs who underwent partial pancreatic resection. Time to last follow-up was defined as the number of months between the date of initial interventions for diagnosis (surgery or EUS-FNA) and the last date of available follow-up or the date of death. Time to recurrence was defined as the number of months between the date of complete resection and the date of tumor recurrence detection. The study protocol was approved by our local Institutional Review Board.

Preoperative evaluation by CT/MRI and/or EUS-FNA

All patients underwent contrast-enhanced CT scan and/or gadolinium-enhanced MRI before definitive management. Preoperative EUS-FNA procedures were performed at the discretion of treating physicians or surgeons for characterization of the lesion seen on CT/MRI and obtaining cyst fluid analysis for clinical decision-making. Informed consent was obtained at the time of EUS-FNA. EUS was performed using linear echoendoscopes (32UA or 32 UX, Pentax Medical Co, Montvale, NJ; GF-UC30P or GF-UC140P, Olympus America, Inc, Center Valley, Pa) with or without radial echoendoscopes (GF-UM20, GF-UM130, or GF-UM160, Olympus America, Inc). FNA was performed using 19-, 22-, or 25-gauge needles (Cook Endoscopy, Winston-Salem, NC or Boston Scientific, Natick, Mass) with the presence of on-site cytopathology. The aspirated fluid was expressed onto 2 glass slides; 1 was air dried for rapid staining and on-site review and 1 was alcohol fixed for future review. Performance of additional passes to obtain more fluid was left to the discretion of the endosonographer and the cytopathologist based on preliminary review of specimen adequacy.

Cyst fluid analysis

After sufficient material was allocated for cytology, acquisition of cyst fluid for carcinoembryonic antigen, amylase, or molecular analysis (PathFinderTG/Pancreas; RedPath Integrated Pathology, Inc, Pittsburgh, Pa) was performed at the discretion of the endosonographer. Molecular analysis included cyst fluid DNA quantity and quality, K-*ras* point mutation, and tumor suppressor genes (loss of heterozygosity).

Definitive management

After BD-IPMNs were diagnosed on imaging studies (CT/MRI and/or EUS-FNA), surgical resection was recommended if symptoms were pancreatic in nature (abdominal pain of pancreatic nature, acute pancreatitis, and unexplained weight loss) or suspicious features for malignancy were found on preoperative evaluation and patients were fit for surgery. Before 2006 suspicious features for malignancy included cyst size $\geq$ 3 cm, MPD dilation ($\geq$10 mm), presence of solid component, cytologic evidence of high-grade dysplasia, or cytology definitive for malignancy. For BD-IPMNs diagnosed during 2006 to 2012 and after 2012, suspicious features for malignancy were based on the ICG 2006 and the ICG 2012, respectively. Surgical resections were performed by 1 of 4 experienced pancreaticobiliary surgeons. After surgical resection, CT, MRI, and/or EUS was performed periodically for surveillance. When patients were deemed poor surgical candidates, pancreatic cyst epithelial ablation with ethanol with or without paclitaxel injection was performed based on treating physician and patient preferences as previously described.[17] For asymptomatic patients, imaging surveillance with EUS and CT/MRI was considered every 3 to 12 months as appropriate based on risks for malignancy. Since 2008, patients were rigorously followed within the Indiana University multidisciplinary pancreatic cyst program.

Statistical analysis

To compare patient and lesion characteristics between groups, the Student *t* test was performed for continuous variables and χ^2 or the Fisher exact test for categoric variables. Continuous variables are reported as mean $\pm$ standard deviation and categoric variables as number and percentage. Using surgical pathology as the reference standard, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of predictive factors for identifying malignant behaviors that proved to be significantly different between the benign and malignant groups. In patients who achieved complete resection, we defined recurrence rates as a time-to-event outcome using the Kaplan-Meier method and compared the survival of benign and malignant BD-IPMNs using a log-rank test. A P value $< .05$ was considered statistically significant. Statistical analyses were performed by using SPSS 16.0 for Windows software (SPSS, Chicago, Ill).

RESULTS

Patient characteristics

During the 13-year study period we identified 364 patients with pure BD-IPMNs; 229 underwent imaging surveillance and 135 underwent surgical resection (Fig. 1, Table 1). Compared with patients managed conservatively, those surgically resected were more frequently found to be smokers and symptomatic at time of diagnosis. Mean time from diagnosis to surgery was 8.5 $\pm$ 13.3 months. On CT/MRI and EUS studies, BD-IPMNs resected were larger in size and less frequently multifocal. However, mean MPD size was not different between groups. Of 364 patients, HRS and WFs (according to the ICG 2012) were identified on CT/MRI in 2% and 34%, respectively; the remainder were non-WF patients (64%).

Indications for surgery based on the ICG 2012

Among the 135 resected BD-IPMNs, 117 were benign lesions (low-grade dysplasia in 81 and moderate-grade dysplasia in 36), whereas 18 were malignant (high-grade dysplasia in 11, minimally invasive cancer in 5, and grossly invasive cancer in 2). The presence of HRS and WFs on CT/MRI was similar between the benign and malignant groups, but the presence of MPD size 5 to 9 mm was more frequently associated with malignancy (Table 2). Compared with benign BD-IPMNs, EUS-FNA features suspicious for malignancy were more frequently detected in malignant lesions, including definite mural nodules, MPD features suspicious for involvement, and suspicious/positive cytology for malignancy.

EUS features and cyst fluid analysis

Of 135 BD-IPMN patients managed surgically, EUS-FNA was performed in 105 (78%): 91 (78%) in benign and 14 (78%) in malignant lesions (Table 3). Compared with the benign group, patients with malignant lesions had greater mean MPD size, more frequent detection of mural nodules, and larger mean mural nodules size. Nevertheless, cyst diameter, increased cyst size over time before resection, multifocality, cyst location, cyst morphology (the presence of thickened wall, solid component, septations, calcifications, and internal debris), and associated benign-appearing lymphadenopathy were similar between groups. On cyst fluid analysis, median carcinoembryonic antigen and amylase, elevated DNA quantity, poor DNA quality, presence of K-*ras* point mutation, and loss of heterozygosity were not different between groups.

Performance characteristics of preoperative EUS-FNA for identifying malignant BD-IPMNs

Given the association between malignancy and the presence of MPD 5 to 9 mm on CT/MRI, as well as other EUS features, performance characteristics were calculated for these variables. Using surgical pathology as the reference standard, we calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MPD dilation (5-9 mm) on CT/MRI for identifying malignancy and EUS features suspicious for malignancy (Table 4). Mural nodules identified by EUS were missed

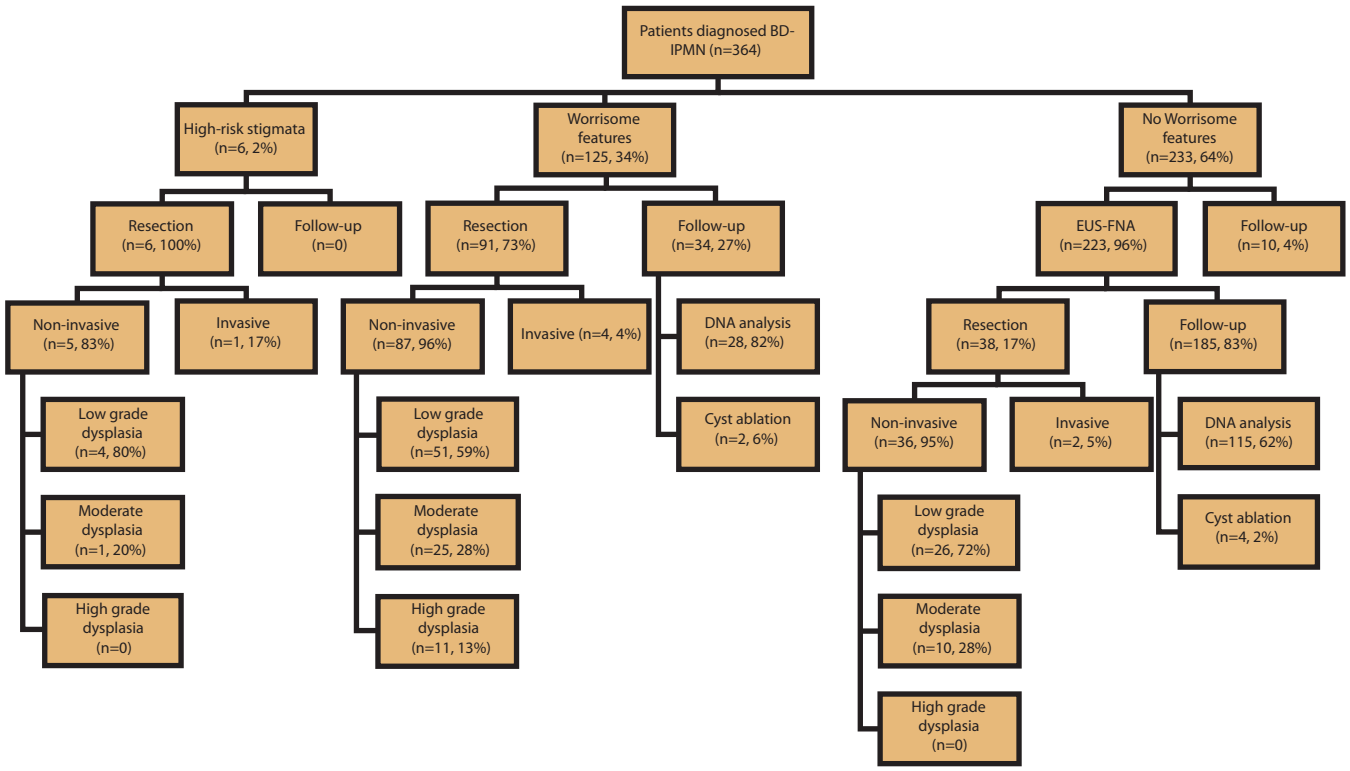

Figure 1. Patient-diagnosed BD-IPMNs during 2001 to 2013 based on ICG 2012 for the management of IPMN and MCN of the pancreas (n = 364).

by CT/MRI in 4 in the benign group (4%; size 5 mm) and 4 in the malignant group (28%; size 6-8 mm).

Long-term outcomes of patients managed surgically

Of 364 patients with BD-IPMNs, all 6 patients with HRS underwent surgery. Five had preoperative EUS-FNA with benign cytology, which was confirmed as benign at surgery. One had malignant cytology and was staged as aT3N0M0 malignancy. This patient underwent a 1-month course of neoadjuvant chemotherapy and died because of postoperative adverse events. Of 125 patients with WFs, 91 (73%) were managed surgically; 76 (84%) had benign disease, and 15 (16%) had malignancy (high-grade dysplasia in 11 and invasive cancer in 4). After surgery, recurrent cystic lesions (with benign cytology) occurred in 8 and 3 patients in the benign and malignant groups, respectively. Among 233 patients with no WFs on CT/MRI, 223 (96%) underwent EUS-FNA and 10 (4%) underwent EUS without FNA. After EUS-FNA (n = 223), 38 patients (17%) underwent surgery: 30 patients presenting with concerning symptoms and/or increased cyst size had benign cytology and histopathology, 6 patients had suspicious cytology for malignancy but benign histopathology upon resection, and 2 patients were found to have mural nodules on EUS but missed by MRI and invasive malignancy proved on surgical pathology.

Among 135 patients undergoing surgical resection, mean time from diagnosis to surgery and choice of operation were similar in the benign and malignant groups (Table 5). Mean length of stay, 30-day postoperative morbidity, and 30-day mortality did not differ between groups. Death related to surgery occurred in 7 patients. Based on surgical pathology, complete resection was achieved in 95% and 100% of the benign and malignant groups, respectively. In benign BD-IPMNs with incomplete resection (n = 6), all had low-grade dysplasia at the surgical margin and continued to be surveyed by imaging with stable lesion size during follow-up. After surgery, 15 patients with benign lesions were lost to follow-up. Mean duration of follow-up was not different between the benign and malignant groups. During a median follow-up period of 48 months (range, 6-160), no patient died from pancreatic cancer but 10 died from unrelated causes.

Long-term outcomes of patients managed conservatively

Of 34 patients with WFs undergoing imaging surveillance, stable cyst size was identified in 27 patients (79%), increased cyst size (benign cytology/molecular behavior) in 3 (9%), and cyst ablation with and without response in 1 (3%) and 1 (3%), respectively. Two patients with WFs were lost to follow-up after their first surveillance.

TABLE 1. Baseline characteristics at time of diagnosis in patients with BD-IPMN (n = 364)

Baseline characteristics	Conservative (n = 229)	Surgery (n = 135)	*P* value
Mean age, y, ± SD	67.1 ± 12.2	65.2 ± 12.5	.16
Female, n (%)	136 (59)	64 (47)	.04
Mean body mass index, kg/m^2, ± SD	27.7 ± 5.4	27.7 ± 4.5	1.00
Clinical presentations, n (%)			
Incidental finding	164 (72)	35 (26)	<.001
Acute pancreatitis	21 (9)	36 (27)	<.001
Abdominal pain of pancreatic nature	50 (22)	83 (61)	<.001
Nausea/vomiting	3 (1)	18 (13)	<.001
Weight loss	13 (6)	23 (17)	.001
Family history of pancreatic cancer, n (%)	19 (8)	8 (6)	.53
Smoking,* n (%)	45 (20)	57 (42)	<.001
Alcohol drinking,† n (%)	34 (15)	16 (12)	.52
Diabetes, n (%)	33 (14)	20 (15)	.45
History of chronic pancreatitis, n (%)	19 (8)	15 (11)	.48
Laboratory findings (mean ± SD)			
Serum lipase (n = 227)	41.6 ± 33.4	45.7 ± 32.5	.35
Serum alkaline phosphatase (n = 273)	73.8 ± 27.1	77.9 ± 32.4	.27
Serum Hb_{A1c} (n = 156)	6.2 ± .9	6.3 ± 1.2	.27
Serum carcinoembryonic antigen (n = 99)	2.2 ± 2.0	6.1 ± 26.1	.30
Serum CA19-9 (n = 210)	30.6 ± 58.7	33.4 ± 106.2	.81
CT/MRI performed, n (%)	229 (100)	135 (100)	
Mean cyst size, cm, ± SD	1.9 ± 1.7	2.6 ± 1.6	<.001
Mean MPD size, mm, ± SD	3.3 ± 1.3	3.8 ± 2.6	.53
Multifocal lesions, n (%)	129 (56)	48 (35)	<.001
EUS performed, n (%)	229 (100)	106 (78)	<.001
Mean cyst size, cm, ± SD	1.9 ± 1.2	2.9 ± 2.5	<.001
Mean MPD size, mm, ± SD	3.2 ± 1.9	3.4 ± 1.7	.46
Molecular analysis, n (%)	183 (80)	35 (26)	<.001

BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; *SD*, standard deviation; *MRI*, magnetic resonance imaging; *MPD*, main pancreatic duct.
*Smoking a pack per day for at least 20 years.
†Eight drinks or more per week for women and 15 drinks or more per week for men.

Of 185 non-WF patients undergoing imaging surveillance after benign or inconclusive cytology on EUS-FNA, stable cyst size was observed in 166 patients (90%), increased cyst size (benign cytology/molecular analysis) in 14 (8%), and cyst ablation with and without response in 3 (2%) and 1 (1%), respectively. One had distinct pancreatic adenocarcinoma with liver metastasis detected by EUS after 22 months of follow-up; however, MRI did not show any new lesions at 3 and 18 months earlier. No patient was lost to follow-up in this group. Of 10 patients undergoing EUS without FNA, 4 had stable cyst size on imaging surveillance and 6 were lost to follow-up.

Of 6 patients undergoing cyst ablation, 4 had good response with cyst involution and symptom resolution but 2 had mild pancreatitis after the procedure. No patient undergoing cyst ablation developed cancer during follow-up.

Tumor recurrence rates

Analysis limited to patients with complete resection demonstrated recurrence to be more frequently observed in malignant BD-IPMNs (Table 5). Time to recurrence ranged from 4 to 39 months for the benign group and from 4 to 90 months for the malignant group. Recurrent tumors were found at the resection margin in the pancreatic body in 2 patients, 1 identified in the benign group and 1 in the malignant group. All patients with recurrence had benign cytology at surveillance EUS-FNA, and no patient underwent a second surgery. When we used the Kaplan-Meier method, patients with malignant BD-IPMNs had higher risk of recurrence during a mean follow-up period of 131 months ($P = .01$); recurrent tumors occurred as early as 34 months and as late as 94 months after the primary tumor was resected (Fig. 2).

TABLE 2. Indications for surgery in patients with BD-IPMNs based on International Consensus Guidelines 2012 for the management of BD-IPMNs of the pancreas

Indications	Benign (n = 117)	Malignant (n = 18)	*P* value
HRS on CT/MRI			
MPD diameter ≥ 10 mm	2 (2)	0	1.00
Enhanced solid component	3 (3)	1 (5)	1.00
WFs on CT/MRI			
MPD size 5-9 mm	21 (18)	9 (50)	.01
Cyst size ≥ 30 mm	33 (28)	5 (28)	1.00
Thickened enhanced cyst walls	2 (2)	1 (5)	1.00
Nonenhanced mural nodules	2 (2)	1 (5)	1.00
Abrupt change in the MPD caliber with distal pancreatic atrophy	0	0	
Features on EUS-FNA (n = 105)			
Definite mural nodules*	6 (6)	5 (36)	.01
MPD features suspicious for involvement†	9 (10)	5 (36)	.01
Suspicious/positive cytology for malignancy	8 (9)	4 (29)	.04

Values are number of cases with percents in parentheses.
BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; *MRI*, magnetic resonance imaging; *MPD*, main pancreatic duct; *HRS*, high-risk stigmata; *WF*, worrisome feature.
*Lack of mobility, adherence to the cyst wall, presence of Doppler flow, lack of echogenic stratification seen in mucous aggregates, and/or FNA of nodule itself confirming the presence of tumor tissue.
†Presence of any of the following criteria: thickened walls, intraductal mucin, or mural nodules is suggestive of MPD involvement.

DISCUSSION

Although several studies demonstrated the association between imaging features and malignant BD-IPMNs, these data were limited by small-size series; heterogeneity of the imaging modalities; lack of long-term follow-up, particularly in patients undergoing imaging surveillance; and limited assessment of tumor behavior with EUS-FNA.[4-10,18,19] In a previous study from our group, the type and number of ICG WFs and HRS carried unequal weight and were not cumulative in the prediction of risk of malignancy in IPMNs.[20] Although the cohort of patients followed in that study overlaps with the current one, the present study included many additional patients with BD-IPMNs who underwent imaging surveillance. In the present study we determined the association between malignant BD-IPMNs and HRS/WFs on CT/MRI based on the ICG 2012 and specifically evaluated EUS characteristics of malignant BD-IPMNs. Further, we present extended and rigorous follow-up of patients within our multidisciplinary pancreatic cyst program. Among HRS and WFs on CT/MRI, MPD size 5 to 9 mm was associated with malignant lesions, whereas EUS features were strongly associated with malignancy, including definite mural nodules, MPD features suspicious for involvement, and suspicious/malignant cytology. A possible explanation may be the limitation of CT/MRI in identifying features associated with malignancy in BD-IPMNs, particularly mural nodules.[21] Interestingly, we observed that 28% of mural nodules detected by EUS were missed by CT/MRI in the malignant group, with cyst sizes ranging between 2.1 and 3.5 cm. Among the malignant mural nodules missed by CT/MRI (n = 4), 2 did not have any WFs. In addition to the presence of mural nodules associated with malignant lesions, our study confirms the association of the mean size of the mural nodule on EUS with malignancy (1.7 mm vs 3.7 mm, $P = .02$). Although previous series demonstrated nodule size > 7 to 10 mm on EUS to be strongly associated with malignancy,[8,11,15,22] we detected significantly smaller mural nodules in malignant BD-IPMNs.

Based on the new AGA guidelines, 8 patients were considered low-risk individuals (AGA negative) based on CT/MRI (cysts < 3 cm without a solid component or a dilated pancreatic duct), but EUS identified HRS/WFs (EUS positive) and led to resection. Of these 8 "AGA-negative/EUS-positive" patients, 2 were found to have mural nodules on EUS missed by MRI and with invasive malignancy proved on surgical pathology, whereas 6 had cytology results suspicious for malignancy with benign histopathology at resection. Although the ICG 2012 and recent AGA guidelines recommend a more conservative approach in patients without WFs with a cyst size of 2 to 3 cm, our observations showed 2 of 38 patients (5.3%) in this group who underwent surgery because of mural nodules (found only on EUS), with minimally invasive cancer found at surgery. Although both ICG 2012 and AGA guidelines regard a cyst ≥ 3 cm as a WFs, we reported malignancy in smaller lesions (mean cyst size 2.9 cm vs 2.2 cm in the benign vs malignant group, respectively). Our findings suggest that the evaluation of BD-IPMNs with EUS is likely to influence management options in a significant number of patients by detecting mural nodules

TABLE 3. EUS features and cyst fluid analysis in patients with BD-IPMN who underwent surgery (n = 105)

Cyst characteristics	Benign (n = 91)	Malignant (n = 14)	*P* value
Mean cyst size, cm, ± SD	2.9 ± 2.5	2.2 ± .7	.26
Mean MPD size, mm, ± SD	3.3 ± 1.5	8.5 ± 2.1	<.001
Increasing cyst size, n (%)	13 (14)	2 (14)	1.00
Increased mean size, mm, ± SD	14.1 ± 7.1	27.5 ± 17.7	.47
Mean time to increase size, mo, ± SD	19.8 ± 20.6	12.3 ± 17.0	.64
Locations, n (%)			.70
Proximal pancreas (uncinate, head, and neck)	61 (67)	8 (57)	
Distal pancreas (body and tail)	33 (36)	4 (29)	
Multifocal in proximal and distal	23 (25)	6 (43)	
Multi focal lesions, n (%)	35 (38)	3 (21)	.59
Mural nodules, n (%)	6 (6)	5 (36)	.01
Mean mural nodule size, mm, ± SD	1.7 ± 3.2	3.7 ± 4.1	.02
Thick cyst wall, n (%)	4 (4)	0	.68
Solid component, n (%)	3 (3)	0	1.00
Septations, n (%)	33 (36)	2 (14)	.34
Calcification, n (%)	1 (1)	0	1.00
Internal debris, n (%)	4 (4)	0	1.00
Associated benign-appearing lymphadenopathy	5 (5)	0	1.00
Cyst fluid analysis of clinical indicators			
Amylase, U/L, median (range) (n = 50)	2482 (5-2,300,000)	5015 (246-44,567)	.76
Carcinoembryonic antigen, ng/mL, median (range) (n = 79)	277 (.5-198,960)	261.15 (13.2-221,149)	.37
Cytology suspicious/positive for malignancy, n (%)	8 (9)	4 (29)	.04
Cystic fluid analysis of molecular indicators, n (%)	30 (33)	5 (36)	.74
Elevated DNA quantity*	4 (4)	1 (7)	1.00
Poor DNA quality†	21 (23)	4 (29)	1.00
KRAS point mutation	16 (17)	1 (7)	.20
Tumor suppressor genes (loss of heterozygosity)	2 (2)	1 (7)	.90

BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; *SD*, standard deviation; *MPD*, main pancreatic duct.
*DNA amount was defined as low (0-4 ng/μL), moderate (4-10 ng/μL), mildly elevated (10-40 ng/μL), and greatly elevated (> 40 ng/μL).
†DNA quality referred to the extent of DNA degradation and was measured by quantitative polymerase chain reaction using crossing the threshold value to determine degradation. This number operated in reverse in that 0 to 27.5 was good quality and over 27.5 was poor quality.

TABLE 4. Performance characteristics of predictive indicators for malignancy in patients with resected BD-IPMNs

Predictive factors*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Based on CT/MRI findings				
MPD size 5-9 mm	43.8	80.7	23.3	91.4
Based on EUS features				
Definite mural nodule	33.3	93.6	40.0	91.7
MPD feature suspicious for involvement	41.7	90.4	35.7	92.4
Cytology suspicious/positive for malignancy	33.3	91.3	33.3	91.3

BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; *MRI*, magnetic resonance imaging; *MPD*, main pancreatic duct.
*Calculated for predictive factors that proved to be significantly different between benign and malignant groups (Table 2).

otherwise missed on imaging or malignant cytology in lesions < 3 cm in size.

One of our main goals was to evaluate the performance characteristics of EUS for identifying malignant lesions. Mural nodules, MPD features suspicious for involvement, and cytology suspicious/positive for malignancy were associated with malignant BD-IPMNs with high specificity (94%, 90%, and 91%) and accuracy (86%, 83%, and 82%) but low sensitivity (33%, 42%, and 33%). Recently, a meta-analysis (4 studies, n = 96) on the diagnostic yield

TABLE 5. Outcome of surgery in patients with BD-IPMNs upon long-term follow-up (median, 48 months [range, 6.4-160.3])

Outcome	Benign (n = 117)	Malignant (n = 18)	*P* value
Mean time from diagnosis to surgery, mo, ± SD	8.1 ± 12.7	11.4 ± 16.5	.33
Type of surgery			.67
Pancreaticoduodenectomy	63 (54)	11 (61)	
Distal pancreatectomy	41 (35)	5 (22)	
Middle pancreatectomy	5 (5)	2 (18)	
Total pancreatectomy	4 (4)	0	
Enucleation	4 (4)	0	
Margin resection			
Complete resection	111 (95)	18 (100)	.49
Incomplete resection	6 (6)	0	.69
Mean size of lesion by pathology, cm, ± SD	2.3 ± 1.3	2.6 ± 1.7	.39
Mean length of hospitalization, days, ± SD	10.8 ± 8.1	8.6 ± 5.8	.36
30-Day postoperative morbidity*	28 (24)	2 (11)	.49
30-Day postoperative mortality†	6 (6)	1 (5)	1.00
Mean duration of follow-up, mo, ± SD	53.9 ± 33.5	42.1 ± 26.2	.21
Lost to follow-up	15 (13)	0	.03
Recurrence‡	8 (7)	3 (17)	.03
Location			
Head	5 (62)	0	
Body	2 (25)	2 (67)	
Tail	1 (12)	1 (33)	
Mean size of lesion by CT/MRI/EUS, cm, ± SD	1.6 ± 1.1	1.0 ± .8	
Mean time to recurrence‡	21.5 ± 17.6	46.8 ± 42.7	.19
Clinical follow-up after surgery			
Asymptomatic without recurrence	71 (61)	12 (67)	
Asymptomatic with recurrence	8 (7)	3 (17)	
Asymptomatic with residual tumors	14 (13)	2 (11)	
Deceased due to pancreatic cancer	0	0	
Deceased due to unrelated causes	9 (8)	1 (5)	

Values are number of cases with percents in parentheses, unless otherwise denoted.
BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; *SD*, standard deviation; *MRI*, magnetic resonance imaging.
*Intra-abdominal abscess/fluid collection (3% vs 0%), intraperitoneal bleeding (2% vs 0%), controlled postoperative pancreatic duct leak with conservative treatment (9% vs 11%), delayed gastric emptying time (3% vs 0%), pulmonary embolism (1% vs 0%), wound infection (2% vs 0%), pneumonia (2% vs 0%), and sepsis (3% vs 0%).
†Cardiopulmonary arrest because of coronary artery disease in 2, intraperitoneal bleeding in 2, and severe sepsis with multi-organ failure in 2. One patient with a malignant lesion was found to have intraperitoneal bleeding at autopsy.
‡Limited to patients with complete resection.

of EUS-FNA–based cytology to distinguish malignant from benign IPMNs showed a pooled sensitivity and specificity of 64.8% and 90.6%, respectively. However, data on BD-IPMNs specifically were not available in 3 studies included in the meta-analysis. In a limited number of cases in our study, molecular analysis did not add value to negative or inadequate cytology for identifying malignant behavior in patients with BD-IPMNs, which is consistent with our previous study.[23] Additionally, a meta-analysis (41 studies) reported the risk of malignancy associated with individual cyst features in IPMNs to include a cyst size > 3 cm, presence of a mural nodule, dilatation of the MPD, and main versus branch-duct IPMNs.[24] The other meta-analysis (23 studies) of imaging features to distinguish malignant and benign BD-IPMNs demonstrated strong association between mural nodules and malignancy, warranting surgical resection, whereas a cyst size ≥ 3 cm, MPD dilatation (5-9 mm), or thick septum/wall should be managed with careful observation and/or further evaluation.[5] However, more than 50% of studies included in both meta-analyses used variable imaging modalities, including CT, MRI, or EUS, to assess the lesion characteristics, resulting in significant heterogeneity of the imaging modalities.[5,24]

Consistent with previous series,[9] we report an 8% recurrence rate of BD-IPMNs in the pancreatic remnant

Figure 2. Tumor-free survival after surgical resection comparing patients with benign BD-IPMNs (n = 117) and malignant IPMNs (n = 18) during follow-up (mean 130.7 ± 8.4 months) (P = .01). *Patients without tumor recurrence by the end of the study period.

after surgical resection. Our data showed higher risk of benign-lesion recurrence in malignant BD-IPMNs compared with benign lesions during a mean follow-up period of 131 months (17% vs 7%, P = .03). When we used the Kaplan-Meier method, recurrence was documented in malignant lesions up to 8 years after resection, suggesting the need for long-term surveillance. Our observations demonstrated benign behavior in all patients with recurrent cystic lesions during surveillance, with no main duct involvement developing after a pure BD-IPMN had been resected.

Although the AGA guidelines suggest that patients with increasing lesion size should undergo EUS-FNA, we found no patients in this group developed malignancy in the lesion. Similar to a previous study[9] limited to patients with complete resection, we observed no patients with IPMN-derived pancreatic adenocarcinoma during a median follow-up of 48 months. Several retrospective series reported distinct pancreatic adenocarcinoma in a different segment of the pancreas away from index IPMNs in up to 11% of patients during follow-up.[25-31] We observed 1 patient without WFs with a cyst size increasing by 50% during surveillance (with benign EUS-FNA cytology) who presented with pancreatic adenocarcinoma in a different part of the pancreas with liver metastasis after 22 months. These results highlight the "field-defect concept" and the need for continued imaging surveillance in BD-IPMNs.

We acknowledge some limitations to our study because of its retrospective design and lack of definite criteria for triaging patients to surgery or imaging surveillance, particularly earlier in the study when data on BD-IPMN management were limited. In addition, 3% and 11% of patients were lost to follow-up in the conservative management group and surgical resection group, respectively.

In conclusion, our study further endorses the practice of incorporating EUS in the management of most BD-IPMNs. Its ability to detect mural nodules missed by CT/MRI highlights the limitation of CT/MRI in predicting malignancy in some BD-IPMNs. The high specificity and accuracy of EUS features of malignancy we report herein strongly position EUS-FNA as the optimum tool for diagnosing malignant BD-IPMNs, particularly in patients without WFs and with smaller cysts.

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Abbreviations: AGA, American Gastroenterological Association Institute; BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; HRS, high-risk stigmata; ICG, International Consensus Guidelines; MPD, main pancreatic duct; MRI, magnetic resonance imaging; WF, worrisome feature.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 506.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2016.02.008

Received September 12, 2015. Accepted February 2, 2016.

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Presented at Digestive Disease Week 2015, May 17-19, 2015, Washington, DC (Gastrointest Endosc 2015;81:AB115-16).

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