Management of Branch-duct Intraductal Papillary Mucinous Neoplasms: A Large Single Center Study to Assess Predictors of Malignancy and Long Term Outcomes

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Abstract

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 2001-2013. Main outcome measures included 1) association between high-risk stigmata (HRS)/worrisome features (WF) of the ICG 2012 and malignant BD-IPMNs; 2) diagnostic yield of preoperative EUS-FNA in identifying malignant BD-IPMNs; 3) recurrence and long-term outcomes of BD-IPMNs patients undergoing surgery or imaging surveillance.

Results: Of 364 BD-IPMNs patients, 229 underwent imaging surveillance and 135 underwent surgery. Among the 135 resected BD-IPMNs, HRS/WF on CT/MRI were similar between the benign and malignant groups, but 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/accuracy of 33%/94%/86%, 42%/91%/83% and 33%/91%/82%, respectively. Mural nodules identified by EUS were missed by CT/MRI in 28% in the malignant group. Patients with malignant lesions had higher risk of any IPMN recurrence during mean follow-up period of 131 months (p=0.01).

Conclusions: Among HRS and WF of the ICG 2012, MPD size 5-9 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 WF and those with smaller cysts. Benign IPMN recurrence was observed in a minority of patients up to 8 years after resection.

Keywords: EUS-FNA; Branch-duct intraductal papillary mucinous neoplasms; High-risk stigmata; Worrisome features; Malignancy

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Introduction

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-IPMN, the indications for surgical resection rely on high-risk stigmata (HRS) and worrisome features (WF) on computed tomography (CT) and magnetic resonance imaging (MRI).[3] Endoscopic ultrasound-fine needle aspiration (EUS-FNA) has been increasingly utilized for the characterization of BD-IPMN lesions but its overall impact on the management of this disease remains unclear. Other imaging modalities like CT and MRI remain the first line of investigations in the majority of patients with an expanding body of literature backing this practice.[4-10]

EUS has been suggested to be the most reliable tool for the characterization of IPMNs.[11] The ICG 2012 recommends possible EUS-FNA for evaluation of small BD-IPMNs without WF only in centers with expertise in EUS-FNA and cytological 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 suggest that pancreatic cysts with at least 2 high-risk features, such as size ≥ 3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA; while 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] Due to this and the lack of consistency across the current guidelines, the utility of EUS in the management of BD-IPMN remains controversial compared to other imaging modalities. While 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: 1) to evaluate the association between image-defined HRS and WF from ICG 2012 and malignant BD-IPMNs; and 2) to determine the diagnostic yield of pre-operative EUS-FNA in identifying malignant BD-IPMNs. The secondary objectives were: 1) to measure recurrence rates of BD-IPMNs after resection during long term follow-up; and 2) to assess long term outcomes in BD-IPMNs 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 main pancreatic duct (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/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), 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. Patients' clinical course was reviewed following surgery if performed and clinical/imaging follow-up if not. Using surgical pathology, lesions were classified as benign (including low- or moderate-grade dysplasia) and malignant (high-grade dysplasia or invasive cancer) based on the World Health Organization (WHO) classification.[16] For the purpose of study analysis, individual risks of malignancy were re-classified 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/EUS and were 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 margin 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/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.

Pre-operative evaluation by CT/MRI and/or EUS-FNA

All patients underwent contrast enhanced CT scan and/or gadolinium-enhanced MRI prior to definitive management. Pre-operative 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 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., Center Valley, PA). FNA was performed using 19-, 22- or 25-gauge needles (Cook Endoscopy, Winston-Salem, NC or Boston Scientific, Natick, MA) with the presence of on-site cytopathology. The aspirated fluid was expressed onto 2 glass slides; one was air dried for rapid staining and on-site review and the other 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 (CEA), amylase, or molecular analysis (PathFinderTG/Pancreas; RedPath Integrated Pathology, Inc., Pittsburgh, Pennsylvania, USA) was performed at the discretion of the endosonographer. Molecular analysis included cyst fluid deoxyribonucleic acid (DNA) quantity and quality, KRAS point mutation and tumor suppressor genes (loss of heterozygosity [LOH]).

Definitive management

Following BD-IPMNs 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 pre-operative evaluation and patients were fit for surgery. Before 2006, suspicious features for malignancy included cyst size ≥ 3 cm, MPD dilation (≥ 10 mm), presence of solid component, cytologic evidence of high-grade dysplasia, or cytology definitive for malignancy. When BD-IPMNs were diagnosed during 2006-2012 and after 2012, suspicious features for malignancy were based on the ICG 2006 and the ICG 2012, respectively. Surgical resections were performed by one of four experienced pancreaticobiliary surgeons. Following 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's preferences as previously described.[17] For asymptomatic patients, imaging surveillance with EUS and CT/MRI was considered every 3-12 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's t-test was performed for continuous variables and chi-square or Fisher's exact test for categorical variables. Continuous variables

were reported as mean±standard deviation (SD). Categorical variables were presented as number and percentages. Using surgical pathology as the reference standard, we calculated sensitivity/specificity/positive predictive value (PPV)/negative predictive value (NPV)/accuracy of predictive factors for identifying malignant behaviors that proved to be significantly different between benign and malignant group. 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 < 0.05 was considered statistically significant. Statistical analyses were performed by using SPSS 16.0 for Windows software (SPSS, Chicago, Ill., USA).

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 (Figure 1 and Table 1). Compared to patients managed conservative, 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±13.3 months. On CT/MRI/EUS studies, BD-IPMNs resected were larger size and less frequently multifocal. However, mean MPD size was not different between groups. Of 364 patients, HRS and WF 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 WF on CT/MRI was similar between the benign and malignant groups, but the presence of MPD size 5-9 mm was more frequently associated with

malignancy (Table 2). Compared to 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 to 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 prior to 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 CEA and amylase, elevated DNA quantity, poor DNA quality, presence of KRAS point mutation, and LOH were not different between groups.

Diagnostic yields of preoperative EUS-FNA for identifying malignant BD-IPMNs

Given the association between malignancy and the presence of MPD size of 5-9 mm on CT/MRI as well as other EUS features, performance characteristics were calculated for these variables. Using surgical pathology as the reference standard, the sensitivity, specificity, PPV, NPV and accuracy of MPD dilation (5-9 mm) on CT/MRI for identifying malignancy and EUS features suspicious for malignancy were calculated (Table 4). Mural nodules identified by EUS were missed by CT/MRI in 4 (4%; size 5 mm) and 4 (28%; size 6-8 mm) in benign and malignant group, respectively.

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

staged as aT3N0M0 malignancy. This patient underwent 1-month course of neoadjuvant chemotherapy however, the patient did not survive post-operative complications . Of 125 patients with WF, 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). Following 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 WF on CT/MRI, 223 (96%) underwent EUS-FNA and 10 (4%) underwent EUS without FNA. Following EUS-FNA (n=223), 38 (17%) underwent surgery; 30 patients presenting with concerning symptoms and/or increased cyst size had benign cytology and histopathology whereas 6 patients had suspicious cytology for malignancy but benign histopathology upon resection. The remaining 2 patients were found to have mural nodules on EUS but missed by MRI and invasive malignancy proven 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 post-operative 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. Following 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 whereas 10 died from unrelated causes.

Long term outcomes of patients managed conservatively

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

Of 185 non-WF patients undergoing imaging surveillance following benign or inconclusive cytology on EUS-FNA, stable cyst size, increased cyst size (benign cytology/molecular analysis), cyst ablation with and without response were observed in 166 (90%), 14 (8%), 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 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, 4/6 had good response with cyst involution and symptom resolution; however, 2/6 had mild pancreatitis following 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 and from 4 to 90 months for benign and malignant group, respectively. Recurrent tumors were found at the resection margin in the pancreatic body in 2 patients; one identified in the benign group and the other in malignant group. All patients with recurrence had benign cytology at surveillance EUS-FNA and no patient underwent a second surgery. Using the Kaplan Meier method**,** patients with malignant BD-IPMNs had higher risk of recurrence during mean follow-up period of 131 months (p=0.01); recurrent tumors occurred as early as 34 months and as late as 94 months after the primary tumor was resected (Figure 2).

Discussion

- Although several studies demonstrated the association between imaging features and malignant BD-IPMNs, these data were limited by small size series, the heterogeneity of the imaging modalities, the 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 IPMN.[20] Although the cohort of patients followed in that study overlaps with the current one, the present study included additional 194 patients with BD-IPMN who underwent imaging surveillance. Moreover, the current study identified a pure cohort of patients with branched duct disease, the management of which represents a challenge given the prevalence of SB-IPMN and the lower risk of malignancy compared to main duct disease.

In the present study, we determined the association between malignant BD-IPMNs and HRS/WF 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 WF on CT/MRI, MPD size 5-9 mm was associated with malignant lesions, while 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 size ranging between 2.1-3.5 cm. Among the malignant mural nodules missed by CT/MRI (n=4), 2 did not have any WF. In addition to the presence of mural nodules that were associated with malignant lesions, our study confirms the association of mean size of the mural

nodule on EUS with malignancy (1.7 mm vs. 3.7 mm, p=0.02). While previous series demonstrated nodule size >7-10 mm on EUS being 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 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/WF (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 proven on surgical pathology; whereas 6 had suspicious cytology for malignancy with benign histopathology at resection. While the ICG 2012 and recent AGA guidelines recommend a more conservative approach in patients without WF with cyst size 2-3 cm, our observations showed 2/38 (5.3%) patients in this group who underwent surgery due to 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 one of WF, 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 on management options in a significant number of patients by detecting mural nodules otherwise missed on imaging or malignant cytology in lesions under 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 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 three 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, one recent meta-analysis (41 studies) reported the risk of malignancy associated with individual cyst features in IPMN to include cyst size > 3 cm, presence of a mural nodule, dilatation of the MPD and main vs. branch duct IPMN.[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 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 8% recurrence rate of BD-IPMN in the pancreatic remnant following surgical resection. Our data showed higher risk of benign-lesion recurrence in malignant BD-IPMNs compared to benign ones during mean follow-up period of 131 months (17% vs. 7 %, p=0.03). Using 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 has been resected.

Although the AGA guidelines suggest that patients with increasing lesion size should undergo EUS-FNA, we found that no patients in this group to have 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 IPMN lesion in up to

11% of patients during follow-up.[25-31] We observed 1 patient without WF with 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-IPMN. This concept could have future implications on the intensity of surveillance using imaging and tumor markers in some patients and might indeed call continued for long term care of these patients rather than termination of surveillance after periods of cyst stability as recently endorsed by the AGA guidelines. (Reference here AGA guidelines)

- There are some limitations to our study. Inherent to its retrospective design and the period of time it covers, there was variability in the management styles of some patients in the cohort, particularly surgical resection referrals. Despite having lost 3% and 11% of patients to follow up in the conservative and surgical resection groups respectively; we provided long term follow-up on most patients particularly those undergoing imaging surveillance. We also described a unique group of patients with histologic diagnosis of pure BD-IPMNs without MPD involvement when compared to the cross-sectional and EUS imaging.

In conclusion, our study further endorses the practice of incorporating EUS in the management of most SB-IPMNs. Its ability to detect mural nodules missed by CT/MRI highlights the limitation of CT/MRI in predicting malignancy in some BD-IPMN lesions. 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 WF and those with smaller cysts.

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

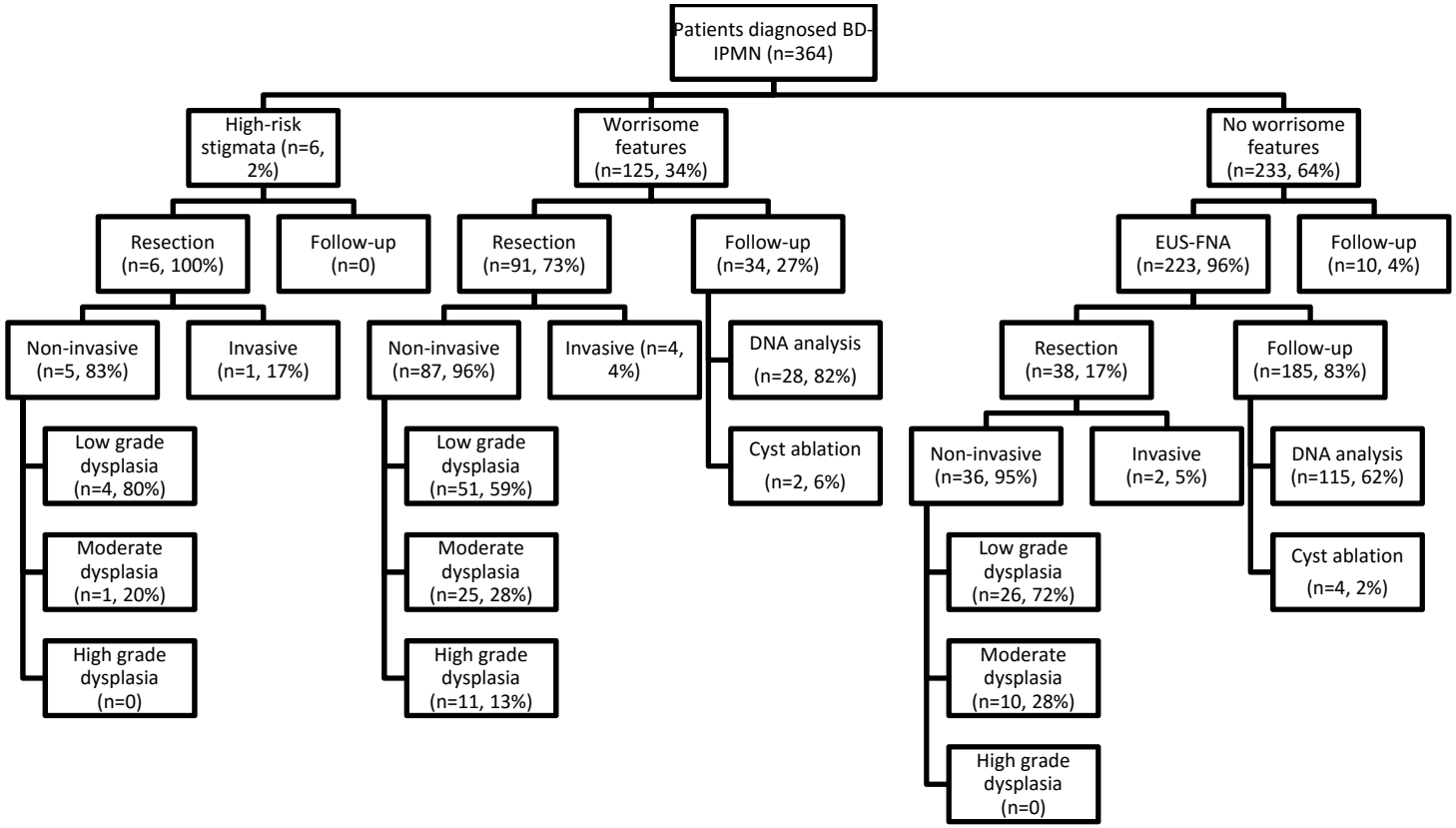

Table 1. Baseline characteristics at time of diagnosis in patients with BD-IPMN (n=364)

Baseline characteristics	Conservative (n=229)	Surgery (n=135)	P value
Mean age (±SD) (years)	67.1±12.2	65.2±12.5	0.16
Female (n, %)	136 (59)	64 (47)	0.04
Body mass idex (±SD) (kg/m^2)	27.7±5.4	27.7±4.5	1.00
Clinical presentations (n, %)			
- **Incidental finding**	164 (72)	35 (26)	<0.001
- **Acute pancreatitis**	21 (9)	36 (27)	<0.001
- **Abdominal pain of pancreatic nature**	50 (22)	83 (61)	<0.001
- **Nausea/vomiting**	3 (1)	18 (13)	<0.001
- **Weight loss**	13 (6)	23 (17)	0.001
Family history of pancreatic cancer (n, %)	19 (8)	8 (6)	0.53
Smoking* (n, %)	45 (20)	57 (42)	<0.001
Alcohol drinking (n, %)**	34 (15)	16 (12)	0.52
Diabetes (n, %)	33 (14)	20 (15)	0.45
History of chronic pancreatitis (n, %)	19 (8)	15 (11)	0.48
Laboratory findings (mean±SD)			
- **Serum lipase (n=227)**	41.6±33.4	45.7±32.5	0.35
- **Serum alkaline phosphatase (n=273)**	73.8±27.1	77.9±32.4	0.27
- **Serum HbA1C (n=156)**	6.2±0.9	6.3±1.2	0.27
- **Serum CEA (n=99)**	2.2±2.0	6.1±26.1	0.30
- **Serum CA 19-9 (n=210)**	30.6±58.7	33.4±106.2	0.81
CT/MRI performed(n, %)	229 (100)	135 (100)	
- **Mean cyst size (±SD) (cm)**	1.9±1.7	2.6±1.6	<0.001
- **Mean MPD size (±SD) (mm)**	3.3±1.3	3.8±2.6	0.53
- **Multifocal lesions**	129 (56)	48 (35)	<0.001
EUS performed(n, %)	229 (100)	106 (78)	<0.001
- **Mean cyst size (±SD) (cm)**	1.9±1.2	2.9±2.5	<0.001
- **Mean MPD size (±SD) (mm)**	3.2±1.9	3.4±1.7	0.46
- **Molecular analysis (n, %)**	183 (80)	35 (26)	<0.001

*Smoking a pack per day for at least 20 years.

**8 drinks or more per week for women and 15 drinks or more per week for men.

Table 2. Indications for surgery in patients with BD-IPMN based on International consensus guidelines 2012 for the management of BD-IPMN of the pancreas

Indications	Benign (n=117)	Malignant (n=18)	P value
High-risk stigmata on CT/MRI (n, %)			
- **MPD diameter ≥ 10 mm**	2 (2)	0	1.00
- **Enhanced solid component**	3 (3)	1 (5)	1.00
Worrisome features on CT/MRI(n, %)			
- **MPD size 5-9 mm**	21 (18)	9 (50)	0.01
- **Cyst size ≥ 30 mm**	33 (28)	5 (28)	1.00
- **Thickened enhanced cyst walls**	2 (2)	1 (5)	1.00
- **Non-enhanced 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, %) (n=105)			
- **Definite mural nodules***	6 (6)	5 (36)	0.01
- **MPD features suspicious for involvement****	9 (10)	5 (36)	0.01
- **Suspicious/positive cytology for malignancy**	8 (9)	4 (29)	0.04

*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

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 (±SD) (cm)	2.9±2.5	2.2±0.7	0.26
Mean MPD size (±SD) (mm)	3.3±1.5	8.5±2.1	<0.001
Increasing cyst size (n, %)	13 (14)	2 (14)	1.00
- **Increased mean size (±SD) (mm)**	14.1±7.1	27.5±17.7	0.47
- **Mean time to increase size (±SD) (months)**	19.8±20.6	12.3±17.0	0.64
Locations (n, %)			0.70
- **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)	0.59
Mural nodules (n, %)	6 (6)	5 (36)	0.01
Mean mural nodule size (±SD) (mm)	1.7±3.2	3.7±4.1	0.02
Thick cyst wall (n, %)	4 (4)	0	0.68
Solid component (n, %)	3 (3)	0	1.00
Septations (n, %)	33 (36)	2 (14)	0.34
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(median, range) (U/L) (n=50)**	2482 (5-2300000)	5015 (246-44567)	0.76
- **CEA (median, range) (ng/mL) (n=79)**	277 (0.5-198960)	261.15 (13.2-221149)	0.37
- **Cytology suspicious/positive for malignancy (n, %)**	8 (9)	4 (29)	0.04
Cystic fluid analysis of molecular indicators (n, %)	30 (33)	5 (36)	0.74
- **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)	0.20
- **Tumor suppressor genes (LOH)**	2 (2)	1 (7)	0.90

*DNA amount was defined as low (0-4 ng/ul), moderate (4-10 ng/ul), mildly elevated (10-40 ng/ul) and greatly elevated (> 40 ng/ul).

**DNA quality referred to the extent of DNA degradation and was measured by quantitative PCR using crossing the threshold value to determine degradation. This number operated in reverse in that 0-27.5 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 (%)	PPV (%)	NPV (%)
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

*Calculated for predictive factors that proved to be significantly different between benign and malignant groups (Table 2)

**In the malignant group, 28% (n=4) of mural nodules detected by EUS were missed by CT/MRI.

Table 5. Outcome ofsurgery in patients with BD-IPMN upon long term follow-up(median 48 months, range 6.4-160.3 months)

Outcome	Benign (n=117)	Malignant (n=18)	P value
Mean time from diagnosis to surgery (±SD) (months)	8.1±12.7	11.4±16.5	0.33
Type of surgery			0.67
- **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)	0.49
- **Incomplete resection**	6 (6)	0	0.69
Mean size of lesion by pathology (±SD) (cm)	2.3±1.3	2.6±1.7	0.39
Mean length of hospitalization (range) (days)	10.8±8.1	8.6±5.8	0.36
30-day post-operative morbidity* (n, %)	28 (24)	2 (11)	0.49
30-day post-operative mortality (n, %)**	6 (6)	1 (5)	1.00
Mean duration of follow-up (±SD) (months)	53.9±33.5	42.1±26.2	0.21
Lost to follow up	15 (13)	0	0.03
Recurrence***	8 (7)	3 (17)	0.03
- **Location**			
Head	5 (62)	0	
Body	2 (25)	2 (67)	
Tail	1 (12)	1 (33)	
- **Mean size of lesion by CT/MRI/EUS (±SD) (cm)**	1.6±1.1	1.0±0.8	

Mean time to recurrence* (n, %)**	21.5±17.6	46.8±42.7	0.19
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)	

*Intra-abdominal abscess/fluid collection (3% vs. 0%), intraperitoneal bleeding (2% vs.0%), controlled postoperative PD 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 due to coronary artery disease in 2, intraperitoneal bleeding in 2, severe sepsis with multiorgan failure in 2. One patient with malignant lesion was found to have intraperitoneal bleeding at autopsy.

***Limited to patients with complete resection

Figure 2. Tumor-free survival after surgical resection comparing patients with benign BD-IPMN (n=117) and malignant IPMN (n=18) during follow-up (mean 130.7±8.4 months) (p=0.01)

*Patients without tumor recurrence by the end of the study period.