

**INCIDENTAL PANCREATIC CYSTS:
DO WE REALLY KNOW WHAT WE ARE WATCHING?**

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Introduction

The diagnostic work-up and management of incidentally discovered cystic lesions of the pancreas (CLPs) continues to evolve. In 2004, the Sendai consensus conference provided guidelines for the management of intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) [1]. It recommended resection for all main-duct IPMNs and MCNs, and 'careful observation' for asymptomatic branch-duct (Bd) IPMNs measuring <30 mm in the absence of solid components or main-duct dilation. Because the majority of incidentally discovered CLPs are felt to be Bd-IPMNs and fit the Sendai criteria, currently many are managed non-operatively with close clinical follow-up and frequent re-imaging. So far, several studies have validated this approach [2, 3, 4], although none of them has yet followed patients long term. A major caveat of these follow-up studies is the lack of a definitive diagnosis in most patients since only few have thus far been resected.

Little is known about the accuracy of the clinician's ability to ascertain the identity of CLPs in advance of tissue confirmation. In an attempt to measure this accuracy, the present study compares the preoperative and final histological diagnoses in a large cohort of incidentally discovered CLPs, as evaluated by various imaging strategies.

Methods

A retrospective review identified 566 patients who were evaluated for a possible cystic neoplasm of the pancreas between January 2000 and January 2008 in the Department of Surgery of the Massachusetts General Hospital. Among these, 330 patients were classified as having incidentally discovered lesions either because they were asymptomatic or because the cyst was noted during imaging of an unrelated problem.

Using electronic hospital records and office charts, relevant clinicopathological information was logged into a Microsoft Access database. The collected data included patients' demographics, details of diagnostic evaluation, presumptive diagnosis, and initial disposition (i.e. surgery or observation). The cysts were measured at their largest diameter on cross-sectional imaging. In those patients who underwent resection, the preoperative clinical diagnosis was compared to the final tissue diagnosis. We specifically avoided re-reviewing available images and pathological blocks a posteriori in order to report our actual experience, rather than an unrealistic best-case scenario.

Data is presented as mean and SD or median and range. Statistical analysis was carried out using the Primer of Biostatistics v6.0 software [5]; t test was used for continuous variables and z test for comparison of proportions. A p value <0.05 was considered statistically significant.

Results

Incidentally discovered cysts were most frequently identified during the work-up of urologic complaints (21%), other gastrointestinal diseases (21%), non-specific abdominal discomfort (17%), thoracic (9%) or gynecologic complaints (4%). The majority (62%) were found in women, and the mean age was 65.8 years. All patients were evaluated with cross-sectional imaging: 76% had a CT and 41% had an MR (19% had both); 52% also underwent endoscopic ultrasound (EUS). Median cyst size was 20 mm (3-130 mm) and multiple lesions were present in 60/330 patients (18%); the median number of lesions in these patients was 4 (range 2-10).

Early Surgical Treatment

At the time of diagnosis, 41% of patients (136/330) with incidentally discovered CLPs underwent resection generally on the basis of the Sendai criteria suggesting concern for potential malignancy. Their characteristics and preoperative diagnosis are shown in table 1. 44% underwent a distal pancreatectomy, 41% a pancreaticoduodenectomy and 15% a middle pancreatectomy or other atypical resection. Operative mortality was zero. The final pathologic diagnoses are shown in table 2. Invasive cancer was found in 9 patients (7%) all of which met Sendai criteria, having either main-duct dilation, a solid component, or size >3 cm; 16 (12%) had either carcinoma in situ or a neuroendocrine neoplasm.

Fifty patients underwent resection for a presumed Bd- IPMN, but only 32 of these (64%) were confirmed as such by histopathology. A main-duct extension was identified in 10 patients (20%), and therefore the final pathological diagnosis was combined-duct IPMN. Figure 1 shows an example of this situation. Two cases were serous cystadenomas (SCA), and 1 was a MCN. The remaining 5 were diagnosed histologically as 'unclassified' benign pancreatic cysts, which are thought to be non-neoplastic.

Table 1

Characteristics and initial disposition

	Surgery	No surgery	p value
Total patients	136	194	
Female, %	60	64	0.5
Mean age \pm SD	61 \pm 15	68 \pm 13	<0.01
Median size (range)	30 (7–130)	15 (3–65)	<0.01
Multifocal cysts (%)	6 (4)	54 (28)	<0.01
Preoperative Dx (%)			
Bd-IPMN	50 (37)	152 (78)	<0.01
MCN	30 (22)	7 (4)	0.5
Md-IPMN	16 (12)	4 (2)	0.7
SCA	12 (9)	20 (10)	0.6
CPEN	8 (6)		
SPPN	4 (3)		
Other	3 (3)	6 (3)	0.06
Cystic PDAC	2 (1)	1 (1)	NS
Uncertain diagnosis ¹	11 (7)	4 (2)	0.3

Characteristics and preoperative diagnosis in 315 patients stratified by initial disposition.

Bd-IPMN = Branch-duct intraductal papillary mucinous neoplasm; MCN = mucinous cystic neoplasm; Md-IPMN = main-duct intraductal papillary cystic neoplasm; SCA = serous cystadenoma; CPEN = cystic pancreatic endocrine neoplasm; SPPN = solid pseudopapillary neoplasm; PDAC = pancreatic ductal adenocarcinoma.

¹ The preoperative diagnosis was not documented.

Histological diagnoses in 136 cystic lesions of the pancreas resected at presentation

Degree of dysplasia		Mucinous neoplasms			Non-mucinous neoplasms				
		Bd-IPMN	Md-IPMN	MCN	SCA	SPPN	CPEN	Uncl.	Other
Benign	Adenoma	17	3	20	22	9	–	6	2
	Borderline	17	11	4					
Malignant	CIS	–	8	–	–		8	–	3
	Invasive	2	3	1					
Sum (% of total)		36 (26)	25 (18)	25 (18)	22 (17)	9 (7)	8 (6)	6 (4)	5 (4)

Bd-IPMN = Branch-duct intraductal papillary mucinous neoplasms; MCN = mucinous cystic neoplasm; Md-IPMN = main-duct intraductal papillary cystic neoplasm; SCA = serous cystadenoma; CPEN = cystic pancreatic endocrine neoplasm; SPPN = solid pseudopapillary neoplasm; Uncl. = unclassified, non-neoplastic cysts; CIS = carcinoma in situ.

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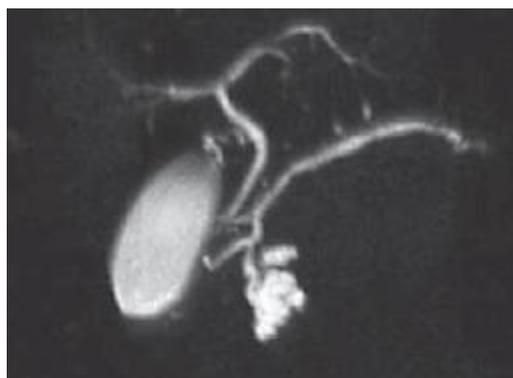


Fig. 1. Magnetic resonance cholangiopancreatography of a 64-year-old female with an incidentally discovered cystic lesion at the uncinus process of the pancreas. The lesion measured 2.7 cm and had no associated nodules; the rest of the pancreas was unremarkable. A presumed diagnosis of Bd-IPMN was made. Because of recent onset of diabetes, and a positive family history for pancreatic cancer, the patient underwent a Whipple's resection. Final diagnosis was combined main-duct and Bd-IPMNs.

Thirty patients were operated on with the preoperative diagnosis of MCN, of which only 18 were confirmed by pathologic examination (60%). The other 12 were: Bd-IPMNs (4), cystic pancreatic endocrine neoplasms (3) (fig. 2), solid-pseudopapillary neoplasms (2), SCA (1), cystic acinar-cell carcinoma (1), and

'unclassified' benign pancreatic cyst (1).

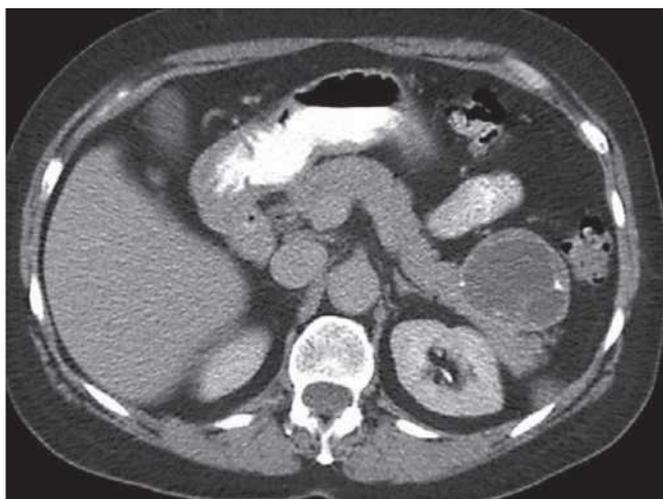


Fig. 2. KT CT scan from a 67-year-old female with an incidentally discovered heterogeneous cystic lesion at the tail of the pancreas measuring 5.2 cm, and with internal calcium deposits. The patient was operated on with a preoperative diagnosis of an MCN, but the final pathology revealed a cystic neuroendocrine neoplasm.

Of the 16 patients presumed to have a main-duct or combined IPMN that were operated on, 15 (94%) were confirmed as such after resection; the other was an MCN.

In 12 patients, the preoperative diagnosis was SCA, and the final histological diagnosis differed in only 1 (MCN).

In 8 patients, the presumed diagnosis was that of a cystic pancreatic endocrine neoplasm (CPEN). This was confirmed by pathology in 4 cases; the remaining were SCAs (2) and solid pseudopapillary neoplasms (2).

Nine patients were thought to have a variety of other diagnoses (including solid pseudopapillary neoplasms, lymphangioma, and pancreatic adenocarcinoma with cystic degeneration), and the diagnosis was accurate only 50% of the time (4/8).

A specific preoperative diagnosis was not documented in 11 patients. Their final histological diagnoses were: MCN (4), SCA (4), solid pseudopapillary tumor (1), CPEN (1), and lymphoepithelial cyst (1).

Overall, in patients operated on at presentation, the clinician accurately predicted the final diagnosis only 68% of the time (fig. 3).

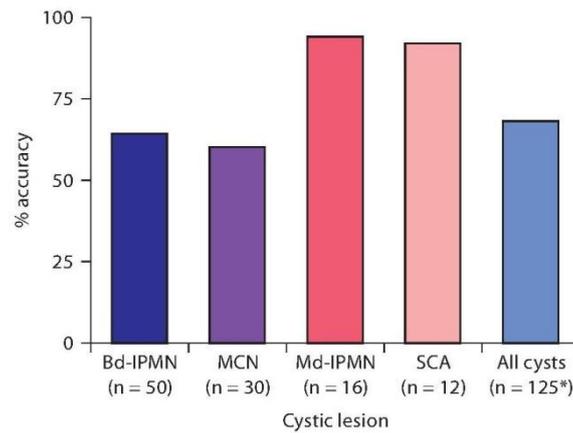


Fig. 3. Accuracy of preoperative diagnosis in 125 incidentally discovered cysts resected at presentation. *Includes 8 cystic endocrine neoplasms, 4 solid pseudopapillary neoplasms, and 5 with various other diagnoses. 11 patients did not have a specific preoperative diagnosis.

Non-Operative Surveillance

194 patients with incidentally discovered pancreatic cysts were initially managed non-operatively, and 179 of them were followed in a surveillance program with annual or semiannual radiological examination. Their clinical characteristics and preoperative diagnoses are listed in table 1. Compared to resected patients, these were older, had smaller cysts, and were seven times more likely to have multifocal cysts. The most common presumed diagnosis was Bd-IPMN 79%, followed by SCA 10%.

Delayed Surgery

Of the 179 patients (13%) in a surveillance program, 23 were eventually operated on after a median follow-up of 23 months (4-90 months). Their characteristics and the reasons for crossover to surgery are detailed in table 3. The most common reason to opt for resection was a significant increase in size. The surgical procedures were: 11 pancreaticoduodenectomies, 11 distal pancreatectomies, and 1 middle pancreatectomy; there was only 1 postoperative death.

During follow-up, the clinician reconsidered the initial diagnosis in 4 patients (17%). In patients who underwent delayed surgery, preoperative and final histological diagnosis matched 52% of the time; the final histological diagnoses are

shown in table 1. Two of these patients were found to have invasive carcinoma after 1.2 and 7.5 years of follow-up, respectively (cases 12 and 22; table 3).

Multifocal Disease

15% (9/60) of patients with multiple cysts underwent resection. Two were presumed to have combined-duct IPMN, and this was confirmed by histological examination. Multifocal Bd-IPMN was the preoperative diagnosis in the remaining 7 cases, however, histological diagnoses confirmed this only in 2 cases. The other 5 were combined-duct-IPMNs (2) and 'unclassified' multifocal benign cysts (3) (fig. 4). The preoperative and final diagnosis matched only 44% of the time.

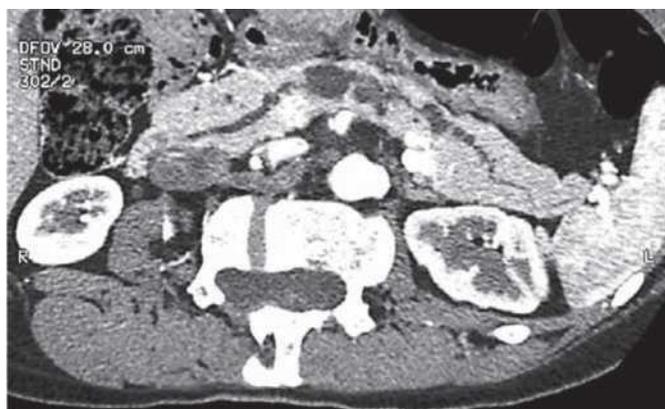


Fig. 4. Reformatted CT images from a 46-year-old female with the incidental discovery of multiple pancreatic cysts during the evaluation of non-specific lower abdominal pain. This was presumed to be multifocal Bd-IPMN or combined IPMN. The suspicion of an associated nodule, and a mildly dilated pancreatic duct to 6 mm, prompted an operation. The final pathological diagnosis was multifocal non-neoplastic cysts.

'Unclassified' Benign Cysts

Eight of 159 (5%) patients operated on for a presumed cystic neoplasm (7 Bd-IPMNs, 1 MCN) were found to have 'unclassified' non-neoplastic cysts. These cysts did not show communication with the ductal system or a mucinous epithelium and are believed to be non-neoplastic.

Table 3

Presentation, diagnosis and indications for resection in 23 patients initially managed with observation

Case	Patient	Initial diagnosis	Dx at the time of surgery	Follow-up months	Reason for resection	Size increase	Tumor markers	Histological diagnosis
1	62 years M; 21 mm cyst/uncinate (additional 19 mm/neck)	Bd-IPMN (multifocal)	same	23	growth	11		IPMN main duct borderline
2	62 years M; 37 mm cyst/body	SCA	same	54	growth	21		serous cystadenoma
3	85 years F, 13 mm cyst/tail	MCN	same	31	growth	7		IPMN branch duct borderline
4	70 years F; 23 mm cyst/tail	Bd-IPMN	same	12	growth	12		serous cystadenoma
5	68 years F; 20 mm cyst/head (additional 2–3 mm cyst/body and tail)	Bd-IPMN (multifocal)	same	39	growth	2		IPMN branch duct adenoma
6	85 years M; 12 mm cyst/head	Bd-IPMN	same	47	growth	21		IPMN branch duct borderline
7	69 years F; 24 mm cyst/head	pseudocyst	combined IPMN	14	growth	16		combined IPMN adenoma
8	71 years M; 29 mm cyst/tail	Bd-IPMN	same	76	tumor markers		CEA: 143 ng/ml + RedPath®	MCN adenoma
9	77 years M; 20 mm cyst/tail		Md-IPMN	87	growth	10		IPMN main duct borderline
10	74 years F; 10 mm cyst/head	Bd-IPMN	same	61	growth	20		IPMN branch duct borderline
11	46 years F; 16 mm cyst/head (additional 5–10 mm cyst/body and tail)	Bd-IPMN (multifocal)	same	10	growth	14		unclassified 'benign' cysts
12	86 years M; 'growing' lesion/head		MCN	15	growth	initial: unknown final: 60 mm		IPMN branch duct invasive
13	54 years F; 'growing' lesion/body and tail	uncertain	uncertain	7	growth	initial: unknown final: 25 mm		serous cystadenoma
14	54 years F; 40 mm cyst/tail		MCN	15	nodule			MCN CIS
15	49 years F; 20 mm cyst/head	Bd-IPMN	same	10	nodule			lymphangioma
16	53 years F; 18 mm cyst/head	MCN	IPMN	8	growth	7		serous cystadenoma
17	24 years M; 20 mm cyst/tail	lympho-epithelial cyst	same	9	growth	10		lymphoepithelial cyst
18	36 years F; 30 mm cyst/tail	SCA	MCN	40	growth	13		MCN adenoma
19	62 years F; 10 mm cyst/body	Bd-IPMN	same	21	tumor markers		CA 19.9: 68 U/ml	IPMN branch duct borderline
20	83 years F; 15 mm cyst/tail	uncertain	uncertain	42	nodule			MCN adenoma
21	63 years F; 20 mm cyst/head	Bd-IPMN	same	4	anxiety			unclassified 'benign' cysts
22	67 years F; 18 mm cyst/tail	Bd-IPMN	MCN invasive	90	nodule			IPMN branch duct invasive
23	64 years F; 27 mm cyst/head	Bd-IPMN	same	23	nodule			combined IPMN – borderline

CEA = Carcinoembryonic antigen; CA 19.9 = cancer antigen 19.9.

Preoperative Test, Size and Accuracy of Diagnosis

The diagnosis was correctly predicted in 63% of cases when cross-sectional (CT or MRI) imaging was used alone; when both studies were done, the accuracy was also 63%. It was not improved in patients who had EUS in addition to either CT

or MRI (69%, $p = \text{NS}$). Only 4 patients were evaluated by the three modalities (CT + MRI + EUS), and only in 2 was the preoperative diagnosis accurate.

Stratifying cysts by size at diagnosis (<30, 31-40, 41-50, >51 mm) did not impact the accuracy of preoperative diagnosis, which was 61, 64, 61, and 60%, respectively ($p = \text{NS}$).

Discussion

The widespread use of high-resolution imaging studies has resulted in detection of unsuspected findings in many organs, and the pancreas is no exception. As a consequence, incidental CLPs are being reported with increasing frequency. A recent study looking at multidetector CT in 2,832 outpatients reported the prevalence of pancreatic cysts as 2.6% [6]. The average size of these cysts was 8.9 mm, and their incidence directly correlated with age. There is concern that a number of these incidentally discovered cysts may represent precursors of pancreatic cancer, such as IPMNs and MCNs, but it is unclear how many of them carry a risk of malignant degeneration, how to identify those accurately, and, once recognized, how to establish which ones are likely to harbor incipient cancer.

The Sendai consensus proposed guidelines for management of IPMNs and MCNs that have been widely adopted in the surgical decision-making process [1]. However, they are based on the premise that we can accurately classify these lesions on the basis of imaging characteristics, an assumption yet to be proven. Through pattern recognition (i.e. demographics, presentation, radiologic appearance, fluid analysis, etc.), a diagnosis is usually reached, but our experience suggests that the histological diagnosis will commonly differ. Although the discrepancy between the preoperative and final diagnosis is unimportant in some cases (e.g. 6-cm cyst in the tail of the pancreas harboring nodules merits resection whether it is a Bd-IPMN, an MCN, or any other cystic neoplasm), in other situations alternative diagnoses might influence the clinician towards either more aggressive or more conservative management (e.g. the management of an asymptomatic 2-cm cystic lesion in the tail of the pancreas without a visible solid component differs if it is believed to be an MCN or a Bd-IPMN).

The present study attempts to provide insight into the presumed accuracy of preoperative diagnosis. In a referral center that currently manages over 100 new patients with CLPs per year, and which has clinicians, endoscopists and radiologists who believe themselves to be very familiar with the differential diagnosis of these lesions, we found that the accuracy of preoperative diagnosis is only 68%, and that it is not the same for all cystic lesions. On the one hand, when the preoperative diagnosis is that of a main-duct IPMN or a SCA, this was almost always correct. On the other hand, when the diagnosis is Bd- IPMN or MCN, the postoperative diagnosis was incorrect about 40% of the time. While it is not surprising that diagnostic overlap exists between these two entities since they have morphologic similarities, misdiagnosis in either direction (i.e. Bd-IPMN that turned out to be MCN, or MCN that was a Bd-IPMN) only accounts for 16% of misdiagnosed cases (5/30). The error in diagnosis does matter, nonetheless, because current recommendations are to resect all MCNs whereas observation is considered appropriate for Bd-IPMN <3 cm. We also found that as many as 20% of presumed Bd-IPMNs have main-duct extension. This is of particular concern because combined Bd- and main-duct IPMNs, like pure main-duct IPMNs, are felt to have an increased likelihood of malignancy [79] (although it is unclear if a microscopic involvement of the main pancreatic duct has the same implications).

On the opposite end of the spectrum, 5% of all resected cysts were histologically diagnosed as non-neoplastic, benign pancreatic cysts. Little is known about these lesions, which have neither mucinous epithelium nor communication with the ductal system. Their radiological characteristics closely mimic and are indistinguishable from Bd-IPMN. They ranged in size between 2 and 3.5 cm, and 50% were multifocal. Had we known that these cysts were non-neoplastic, we would have avoided resection in these asymptomatic patients.

By extrapolating from the preoperative and final histopathological diagnosis in patients with incidentally discovered pancreatic cysts who underwent resection, we attempted to gain insight into the accuracy of diagnosis in the patients managed expectantly. It could be argued that this cannot be done, since the population is

different (older patients with smaller cysts). However, the lack of correlation between preoperative and operative diagnosis was also seen in the 23 patients within the observation group who eventually came to surgery (only 52% accuracy), and we found that neither cyst size nor multifocality (which was more commonly seen in patients managed with observation) influenced this. Inasmuch as the majority of patients with asymptomatic cysts that are being followed have the presumptive diagnosis of Bd-IPMN, it is quite probable that this diagnosis is incorrect in about a third.

This study does not address the issue of which imaging modality is optimal for the differential diagnosis of CLPs. Its retrospective nature, as well as the fact that most patients had only one imaging test and that many of the studies were done in community hospitals with varying techniques and technologies, precludes such a conclusion. We did find that those patients who had both CT and MRI did not have a more accurate preoperative diagnosis. Other than finding a minimal increment in the accuracy of preoperative diagnosis with EUS, our study does not allow us to evaluate its role in refining the diagnosis, or to consider the possible contribution of guided aspiration of cysts for evaluation of the fluid contents. We have previously reported our experience with CEA measurement and cytological fluid analysis [4, 10], and we believe that prospective studies are needed to re-define their role.

In summary, analysis of this large cohort of incidental pancreatic cysts shows that diagnosis based on clinical and radiological information, with or without EUS, is inaccurate in over a third of patients. Some of these have more concerning features than expected, and others, comprising 5% of incidental cysts, are not even neoplastic.

These results underscore the difficulty in preoperative classification of cystic neoplasms of the pancreas with current methods. We continue to face the dilemma of too much versus too little treatment. We do not want to miss the opportunity for cure, but also seek to avoid unnecessary pancreatic resections. In the present state of the art, we await reliable tools, perhaps using new biochemical or genetic markers in the cyst fluid or refinement in radiological imaging [11], that allow for a more precise preoperative diagnosis of incidentally discovered, asymptomatic pancreatic cysts.

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Incidental pancreatic cysts: do we really know what we are watching?

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Background. Most cystic neoplasms of the pancreas (CNPs) are incidentally discovered. Their management continues to be debated and preoperative diagnosis is often inaccurate.

Methods. Retrospective review of 330 patients with incidentally discovered CNPs. Preoperative and final histological diagnoses were correlated.

Results. 41% (136/330) of patients were operated on at diagnosis. 50 patients underwent resection for a presumed branch-duct (Bd) intraductal papillary mucinous neoplasm (IPMN), which was confirmed in only 64% (32/50); of the remaining patients, 20% had main-duct involvement. Mucinous cystic neoplasm was the preoperative diagnosis in 30/136 patients, histologic examination was confirmatory in only 60% (18/30). Most lesions presumed to be main-duct or combined IPMNs or serous cystadenomas were confirmed as such after resection (15/16 and 11/12, respectively). Multifocality was not only associated with Bd-IPMN, and 5% of all cysts were non-neoplastic. Overall, in only 68% of cases did the preoperative and histological diagnoses match.

Conclusions. In an experienced, high-volume center, preoperative diagnosis was incorrect in one-third of incidentally discovered CNPs who underwent resection. Of particular concern, 20% of presumed Bd-IPMN had a main-duct component. Conversely, 5% of resected cysts were not even neoplastic. Clearly, better diagnostic methods are needed to aid in formulating appropriate treatment strategies.