Intraductal Papillary Mucinous Neoplasms
Predictors of Malignant and Invasive Pathology

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Objective: Determine whether size and other preoperative parameters predict malignant or invasive intraductal papillary mucinous neoplasia (IPMN).

Summary Background Data: From 1991 to 2006, 150 patients underwent 156 operations for IPMN.

Methods: Prospectively collected, retrospective review of a single academic institution's experience. All preoperative parameters including a detailed radiologic-based classification of IPMN type, location, distribution, size, number, cytology, and mural nodularity were correlated with IPMN pathology.

Results: Malignant IPMN was present in 32% of cases, whereas 19% of cases were invasive. IPMN type and main pancreatic duct diameter were significant predictors of malignant IPMN ($P < 0.001$). Side-branch lesion number was negatively associated with invasive IPMN ($P = 0.03$). Side-branch size, location, and distribution did not predict IPMN pathology. The presence of mural nodules was associated with malignant and invasive IPMN ($P < 0.001$; $P < 0.02$). Atypical cytopathology was significantly associated with malignant and invasive IPMN ($P < 0.001$; $P < 0.001$). Multivariate analysis demonstrated mural nodularity and atypical cytopathology were predictive of malignancy and/or invasion in branch-type IPMN.

Conclusions: To lower the rate of invasive pathology, surgery should be recommended for fit patients with main-duct IPMN and for branch-duct IPMN with mural nodularity or positive cytology irrespective of location, distribution, or size.

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Intraductal papillary mucinous neoplasms (IPMN) are precancerous pancreatic lesions.[1] They may involve the main pancreatic duct, the branch-ducts, or both. IPMNs, therefore, are classified into 3 types: branch, main, and mixed. The type of IPMN can be predicted by preoperative imaging studies. Magnetic resonance cholangiopancreatography and computed tomography are most often employed to make this distinction; however, endoscopic retrograde pancreatography, endoscopic ultrasound (EUS), intraductal ultrasonography, and peroral pancreatoscopy are more sensitive in making this determination preoperatively.[2–5]

The natural history of IPMN is not known, but previous studies have attempted to stratify risk based on features of the disease. The distinction between main and branch-duct involvement has important implications for cancer risk. When IPMN involves the main-duct, the risk of malignancy (carcinoma in situ or invasive cancer) increases with a reported frequency of 60% to 92%.[6–15] In addition, in the largest collective series of IPMN involving the main-duct, nearly one-third of patients with malignancy were asymptomatic.[6] Based on these data, the current recommendations from the International Consensus Guidelines are resection for all IPMN with main-duct involvement (main- and mixed-type IPMN) in good risk surgical candidates with reasonable life expectancy.[16]

The management of branch-type IPMN has proved to be more complicated. Because of the relatively lower risk of malignant or invasive IPMN, controversy exists regarding the need for surgical resection.[6–18] The International Consensus Guidelines have put forward an algorithm for surgical management, which is based on cyst size, patient symptoms, and "high risk stigmata" (mural nodules, positive cytology). Surgical resection (a) is not recommended in patients with branch-type IPMN <1 cm, (*b*) is recommended in patients with IPMN in the range of 1 to 3 cm if they have symptoms, mural nodules, or positive cytology, and (*c*) is recommended in patients with IPMN >3 cm based on size alone.

Previous studies have examined the correlation of size with IPMN malignancy.[10,13,16,19–24] Some previous series have demonstrated a positive correlation between size and malignant IPMN pathology.[13,16,19–24] Most series, however, combine all IPMN types (branch, mixed, and main) in their size analyses. This methodology skews the analysis and makes it difficult to determine whether branch-duct IPMN size positively correlates with malignancy. This issue prompted

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us to review our experience to determine whether size predicted malignancy or invasion in patients with main or branch-duct IPMN. We also examined the relevance of other preoperative parameters—including cytopathology and the radiographic parameters of type, number, location, distribution, and presence of mural nodularity—in predicting malignancy.[25]

METHODS

Assurance

All data in this study were collected and reported in strict compliance with patient confidentiality guidelines put forth by the Indiana University Institutional Review Board.

Study Population

The patients included in this prospectively collected, retrospective cohort study presented to Indiana University School of Medicine between September 30, 1991, and August 25, 2006. A total of 150 patients underwent 156 pancreatic resections for IPMN. Histories, physical examinations, and preoperative reports were reviewed. All available preoperative imaging, including magnetic resonance cholangiopancreatography, computed tomography, endoscopic retrograde pancreatography, and EUS, was analyzed.

Radiologic Parameters

An intensive review of all available imaging was carried out by 2 readers blinded to final pathology, demographics, or operation performed. The analysis was undertaken using standardized criteria that included IPMN type (main, mixed, or branch), anatomic location of the index lesion, overall distribution, IPMN multiplicity, and size. *Main-type* disease was radiologically defined as dilation of the main pancreatic duct (MPD) with a minimum allowable diameter of 5 mm. *Branch-type* was defined as a lesion characteristic of IPMN with a radiographically identifiable branch-duct connection to the main pancreatic duct. *Mixed-type* was defined as having radiographic characteristics of both main and branch-duct IPMN. The location of the largest lesion (index lesion), the distribution of the lesions, and number of lesions were categorized. In main-duct type index lesion refers to the diameter of MPD dilation. Defined surgical regions included head/uncinate (right of portal vein), neck (overlying portal vein), body (left of portal vein), and tail (left of splenic artery takeoff from celiac axis) of pancreas. IPMN focality was classified as either unifocal or multifocal. Unifocal refers to 1 identifiable branch lesion. Multifocal refers to more than 1 identifiable and distinct lesion. Distribution was defined as localized—confinement within 1 surgical site—or diffuse—including more than 1 surgical site. Main pancreatic duct size was determined by maximal cross sectional diameter (perpendicular to the long axis of the main duct). All measurements of the main pancreatic duct were obtained on images taken before the administration of secretin.

Pathologic Parameters Assessed

All specimens were analyzed by a single faculty pathologist (O.W.C.) experienced in the nomenclature and histopathologic classification of IPMN. The specimens were characterized by World Health Organization IPMN grade (adenoma, borderline, carcinoma in situ [CIS], or invasive). On the basis of operative pathology, patients were classified with malignant/nonmalignant and invasive/noninvasive disease. Adenoma and borderline pathology were considered to be nonmalignant disease, whereas carcinoma-in situ and invasive IPMN were classified malignant. Similarly, adenoma, borderline, and carcinoma in situ were classified as noninvasive whereas invasive adenocarcinoma was classified invasive.

Statistical Methods

Descriptive statistics (frequencies, percentages for categorical data, medians, and interquartile ranges for continuous data) were produced. Comparisons of rates between categorical factors were assessed by the Fisher exact test, whereas group comparisons based on continuous data were performed with the Kruskal-Wallis nonparametric test. The effect of both continuous and categorical factors on dichotomous outcomes (eg, malignant/nonmalignant, invasive/noninvasive) were assessed through a logistic regression analysis and tested by the Wald test. Differences in the malignancy and/or invasiveness rates were described in terms of odds ratios.

RESULTS

Patient Population

During a 15-year period (1991–2006), 150 patients with a diagnosis of IPMN underwent 156 operations at Indiana University Hospital. The mean age at operation was 64 (range 31–84) (Table 1). Patients with main-duct involvement were older (66 vs. 63 [$P = 0.04$]). Gender was nearly equivalent with 77 males and 79 females. Most patients (93%) were symptomatic. Patient symptoms included weight loss (50, 32%), steatorrhea (28, 18%), jaundice (18, 12%), abdominal pain (123, 79%), and nausea/vomiting (60, 38%). Patient conditions included diabetes (29, 19%), and pancreatitis (67, 43%).

The number and type of operations performed were 88 pancreaticoduodenectomies (56%), 45 distal pancreatectomies (29%) (37 open and 8 laparoscopic), 15 total pancreatectomies (10%), and 8 other (5%: included 3 enucleations,[26] 2 central pancreatectomies, 2 exploratory laparoscopies, and 1 exploratory laparotomy). The overall operative morbidity in the entire series was 31%, whereas 30-day mortality was 2.5% (4 patients). The frequency of each dysplastic grade of IPMN as determined by the WHO IPMN classification is shown in Figure 1. Malignant IPMN pathology (ie, invasive and carcinoma in situ lesions) accounted for 50 (32%) of cases, of which 29 (19% overall) were invasive IPMN.

We examined how these patient characteristics correlated with malignant or invasive IPMN pathology. The results are demonstrated in Table 1.

IPMN Type as It Relates to Invasive Pathology

Branch-duct disease without main-duct involvement was found in 103 cases (66%), whereas 53 cases (34%) had main-

TABLE 1. Patient Population, Branch-Type IPMN, and Main-Duct Involvement (Demographics, Symptoms)

Demographics, Symptoms	Population (N = 156 cases*)	Malignant (N = 50)	Nonmalignant (N = 106)	Invasive (N = 29)	Noninvasive (N = 127)	*P*
Patient population						
Age, mean	64	64	64	65	64	NS
Age, median	65	66	64	66	65	NS
% Male population	51	65	45	71	47	0.04†, 0.02‡
Symptoms	145 (93%)	47 (94%)	98 (93%)	26 (90%)	119 (94%)	NS
Symptoms no. (mean)	2	3	2	3	2	0.01‡, NS‡
Steatorrhea	28 (18%)	17 (34%)	11 (10%)	11 (38%)	17 (13%)	0.0002‡, 0.001‡
Jaundice	18 (12%)	10 (20%)	8 (8%)	7 (24%)	11 (9%)	0.04†, 0.03‡
Weight loss	50 (32%)	25 (50%)	25 (24%)	13 (45%)	37 (29%)	0.03†, NS‡
Branch-type IPMN	Population N = 103 cases*	Malignant N = 20	Nonmalignant N = 83	Invasive N = 14	Noninvasive N = 89	
Age, mean	63	62	63	62	63	NS
Age, median	62	60	63	60	63	NS
% Male population	49	63	45	62	47	NS
Symptoms	96 (93%)	18 (90%)	78 (94%)	12 (86%)	84 (94%)	NS
Symptoms no. (mean)	2	3	2	2	2	NS
Steatorrhea	16 (16%)	6 (30%)	10 (12%)	4 (29%)	12 (13%)	NS
Jaundice	8 (8%)	3 (15%)	5 (6%)	2 (14%)	6 (7%)	NS
Weight Loss	28 (27%)	8 (40%)	20 (24%)	5 (36%)	23 (26%)	NS
Main-duct involvement	Population N = 53 cases	Malignant N = 30	Nonmalignant N = 23	Invasive N = 15	Noninvasive N = 38	
Age, mean	66	72	72	73	72	NS
Age, median	67	75	72	77	72	NS
% Male population	57	66	46	80	47	0.02‡
Symptoms (any)	49 (92%)	29 (97%)	20 (87%)	14 (93%	35 (92%)	0.07†
Symptoms no. (mean)	3	3	2	3	3	0.07†
Steatorrhea	12 (32%)	11 (37%)	1 (4%)	7 (46.7)	5 (13%)	0.001†, 0.02‡
Jaundice	10 (19%)	7 (23%)	5 (7%)	5 (33%)	7 (13%)	NS
Weight loss	22 (42%)	17 (57%)	5 (22%)	8 (53%)	14 (36.8%)	0.07†

*150 Patients.
†Malignant versus nonmalignant.
‡Invasive versus noninvasive.

duct disease, this group being composed of 40 mixed type (26%) and 13 main-type (8%) IPMN. Branch-type IPMN had the lowest incidence of invasive (14/103, 14%) IPMN pathology (Fig. 2). The highest incidence of invasion (4 of 13, 31%) was in main-type IPMNs. Compared with main-type IPMN, there was a nearly equal incidence of invasion (11 of 40, 28%) in mixed-type IPMN.

In a direct comparison of branch-type versus main IPMN, the odds ratio of invasive (0.350, $P = 0.03$) IPMN pathology suggest that main-type IPMN is 3 times more likely to be invasive compared with branch-type IPMN. In a direct comparison of any main-duct involvement (main and mixed combined) versus branch-type IPMN, the odds ratio of invasive (2.6, $P = 0.02$) IPMN pathology suggests that IPMN with any main-duct involvement is 2.5 times more likely to be invasive compared with branch-type IPMN.

IPMN Location, Distribution as It Relates to Malignant and Invasive Pathology

In *branch-type* IPMN, of 103 total cases, 61 (59%) were unifocal and 42 (41%) were multifocal. The majority (86 [83%]) of branch-type IPMN were localized (isolated to 1 surgical region), but 17 (17%) were diffuse (involving head as well as body/tail regions). Of the localized lesions, head lesions were present in 50 (58%) and body/tail lesions were present in 36 (42%). Location and distribution of branch-type IPMN were correlated with invasive IPMN pathology. Unifocal branch-type lesions were invasive in 18% whereas multifocal lesions were invasive in only 7% ($P = 0.06$). No difference in the incidence of invasive IPMN pathology existed when comparing localized to diffuse lesions.

In *mixed-type* IPMN, of 40 cases, 14 (35%) were unifocal compared with 26 (65%) which were multifocal. The majority of mixed-type IPMN were diffuse, 29 (72%), compared with localized, 11 (28%). In *main-type* IPMN, of 13 cases, 5 (38%) were localized and 8 (62%) were diffuse. In examining the location and distribution of all IPMN types with *main-duct involvement* (main and mixed types combined) and both separately, no significant correlation existed with malignant or invasive IPMN pathology.

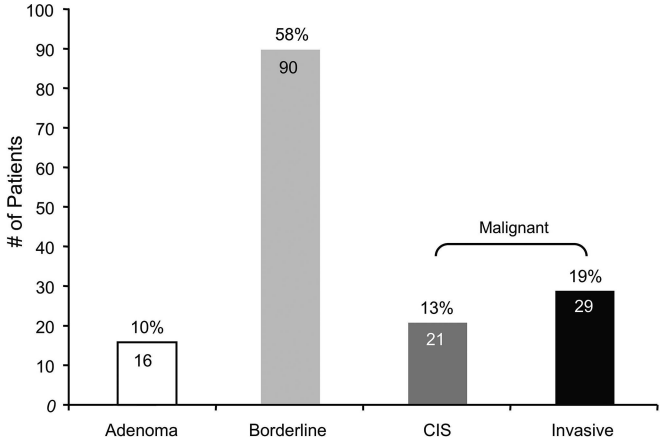

FIGURE 1. Types of IPMN according to dyplastic grade (adenoma, borderline, carcinoma-in situ [CIS] and invasive). Number in each grade shown inside the bar; incidence (%) shown above the bar.

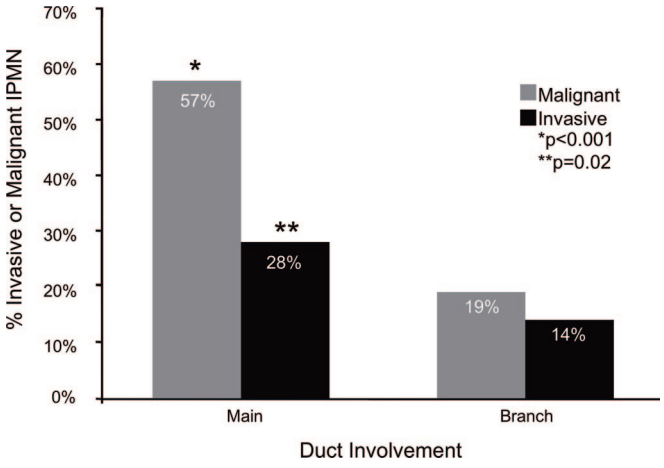

FIGURE 2. Incidence of malignant—*carcinoma-in situ + invasive*—(gray bars) and invasive (black bars) disease according to branch-duct or main-duct (mixed + main) types. ($\div^2$ Test *$P < 0.001$ for malignant vs. nonmalignant; **$P = 0.02$ for invasive vs. noninvasive).

Number of Branch IPMN Lesions as It Relates to Malignant or Invasive Pathology

In addition to lesion size, the total number of branch IPMN lesions for each case was calculated (Table 2). The mean number of branch lesions among branch-type IPMNs was 2.7 ± 0.4 in noninvasive versus 1.6 ± 0.3 in invasive ($P = 0.03$). This finding corroborates the trend of multifocal branch-type IPMN being "protective" compared with unifocal branch-type IPMN noted previously. However, the total number of branch lesions among mixed plus branch IPMNs did not correlate with either malignant or invasive pathology.

Size of IPMN as It Relates to Malignant and Invasive Pathology

Mean *branch-type* IPMN size was 2.2 ± 0.1 cm (Table 2). Median branch-type IPMN size was 2.0 (range 0.4–5.8). Mean cross sectional area was 48.3 ± 5.9 cm^2. The relationship between size of IPMN *branch-type* lesions and malignant or invasive IPMN pathology was investigated. Of 20 cases of malignant branch-type IPMN, the mean and median (range) was 2.0 ± 0.3 cm and 1.9 (range 0.4–5.0) cm compared nonmalignant branch-type IPMN (83 cases) with a mean and median of 2.2 ± 0.1 cm and 1.9 (range 0.4–5.8) cm. Of 14 cases of invasive branch-type IPMN, the mean and median was 2.2 ± 0.4 cm and 2.1 (range 0.4–5.0) cm compared with noninvasive branch-type IPMN (89 cases) with a mean and median of 2.1 ± 0.4 cm and 1.8 (range 0.4–5.8) cm. Mean and median size of branch-type IPMN was not associated with malignant or invasive IPMN pathology. Cross-sectional area of branch-type IPMN lesions also was not associated with malignant or invasive IPMN pathology (Table 2).

In addition to the continuous size variables, we also examined multiple size cut-offs including 1, 2, and 3 cm (Table 2). The likelihood of an invasive IPMN being <3 cm (11 of 14, 79%) was the same as a noninvasive IPMN being <3 cm (71 of 89, 80%). Similarly, the <1 cm and <2 cm size cut-offs were not significantly associated with malignancy or invasion. An examination of the size categories used in the International Consensus Guidelines algorithm for the treatment of branch-type IPMN (<1 cm, 1–3 cm, >3 cm) was also performed (Fig.

TABLE 2. Branch-Type IPMN Size and Number According to Pathologic Category

Size	All (103)	Malignant (20)	Nonmalignant (83)	Invasive (14)	Noninvasive (89)	*P*
Mean (cm)	2.2 ± 0.1	2.0 ± 0.3	2.2 ± 0.1	2.2 ± 0.4	2.1 ± 0.1	NS
Median (cm)	2.0	1.9	1.9	2.1	1.8	NS
Area (cm^2)	48.3 ± 5.9	45.5	48.9	57.7	47.1	NS
Size thresholds						
<1 cm	18 (17%)	3 (15%)	15 (18%)	3 (21%)	15 (17%)	NS
>1 cm	85	17	68	11	74	
<2 cm	53 (51%)	11 (55%)	42 (51%)	6 (43%)	47 (53%)	NS
≥2 cm	50	9	41	8	42	
<3 cm	82 (80%)	16 (80%)	66 (80%)	11 (79%)	71 (80%)	NS
≥3 cm	21	4	17	3	18	
No. lesions	2.7 ± 0.4	2.4	2.6	1.5 ± 0.3	2.7 ± 0.4	0.02*

*Invasive versus noninvasive.

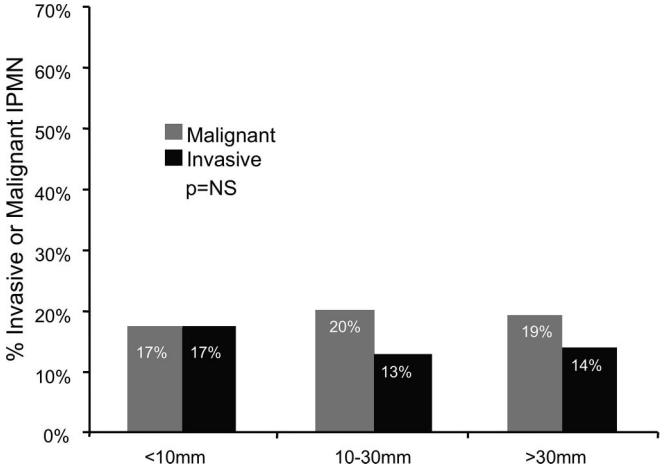

FIGURE 3. Incidence of branch-type IPMN with malignant (gray bars) or invasive (black bars) disease according to International Consensus Guideline (ICG) size categories (Mantel-Haenszel P = NS when assessing malignant and invasive by ICG size category).

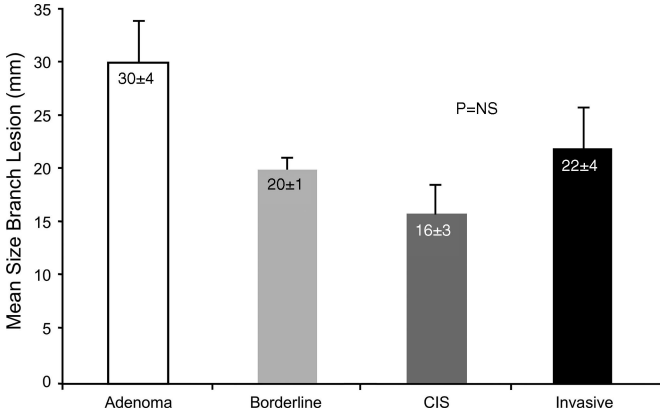

FIGURE 4. Mean (±SEM) size of branch-type IPMN according to dysplastic grade (Kruskal-Wallis $P = 0.133$ when assessing pathology vs. size as a continuous variable).

3). The incidence of malignant and invasive IPMN for <1 cm (17%, 17%) was comparable to 1 to 3 cm (20%, 13%) and to >3 cm (19%, 14%).

Finally, we compared IPMN branch-type size by each WHO pathologic category (Fig. 4). The mean sizes were 3.0 ± 0.4 cm for adenoma, 2.0 ± 0.1 mm for borderline, 1.6 ± 0.3 cm for carcinoma in situ, and 2.2 ± 0.4 cm for invasive IPMN. The median sizes were 2.6 cm for adenoma, 1.8 cm for borderline, 1.2 cm for carcinoma in situ, and 2.2 cm for invasive. None of these differences was statistically significant.

With respect to size of *mixed-type* IPMN, the mean size of branch-type component of the mixed-type IPMNs was not associated with malignant or invasive IPMN pathology ($P = 0.81$; $P = 0.75$).

Main Pancreatic Duct Size as It Relates to Malignant or Invasive Pathology

The mean and median main pancreatic duct size in the entire series was 7.2 ± 0.5 mm and 6.0 (1.3–52) mm. The mean and median main pancreatic duct size in malignant IPMN was 9.6 ± 1.1 mm and 8.8 (1.3–52) mm compared with 5.9 ± 0.4 mm and 4.7 (1.6–16.7) mm for nonmalignant IPMN ($P < 0.001$). In invasive compared with noninvasive IPMN, the mean and median main pancreatic duct size was 8.4 ± 0.8 mm and 7.5 (1.3–19.7) mm and 6.9 ± 0.5 and 5.2 (1.6–52) mm, respectively ($P = 0.02$).

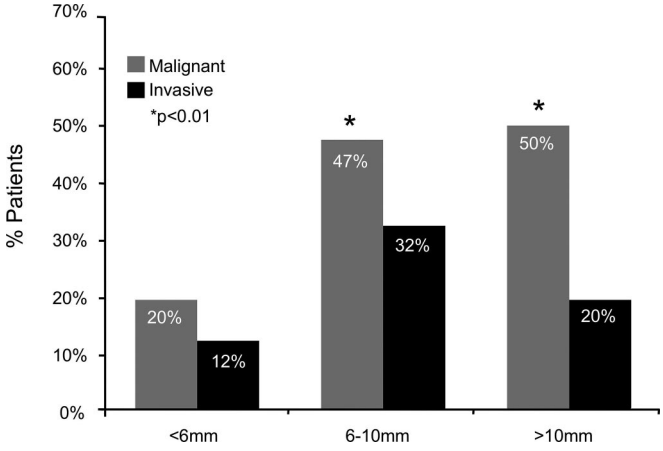

FIGURE 5. Incidence of malignant (gray bars) or invasive (black bars) IPMN according to main-duct diameter ($\div^2$ Test $^*P < 0.01$ for malignant vs. nonmalignant).

In addition to continuous size variables, we also examined multiple size groupings (<6 mm, 6–10 mm, and >10 mm) (Fig. 5). Again, main pancreatic duct size predicted malignant IPMN ($P = 0.004$) but fell short of significance in predicting invasive IPMN ($P = 0.09$). We also compared the size of the main pancreatic duct in cases with main-duct involvement (main and mixed types combined) to cases with isolated branch-type IPMN. This comparison was significant for predicting malignant ($P < 0.001$) and invasive ($P = 0.02$) IPMN. Main pancreatic duct size did not predict malignancy within the subgroup of branch-type IPMN.

Mural Nodules as They Relate to Malignant or Invasive Pathology

Mural nodules were present in 23 (15%) of patients. According to IPMN type, mural nodules were present in 12 (12%) branch-type, 8 (20%) mixed type, and 3 (23%) main-type and 11 (21%) main and mixed types combined. Mural nodules were present in 15 (30%) and 9 (31%) of patients with malignant and invasive IPMN compared with 8 (8%) and 14 (11%) in nonmalignant and noninvasive. Thus, the presence of mural nodule was predictive of malignant/invasive IPMN ($P < 0.001$, $P < 0.02$, respectively).

In cases of *branch-type* IPMN, a mural nodule was present in 6 (30%) and 4 (29%) of patients with malignant and invasive IPMN compared with 6 (10%) and 8 (9%) in nonmalignant and noninvasive. Thus, the presence of mural nodules in branch-type IPMN was predictive of malignant/invasive IPMN ($P < 0.05$, $P = 0.06$, respectively). Figure 6 shows the significant association of mural nodules with dysplastic grade ($P < 0.008$).

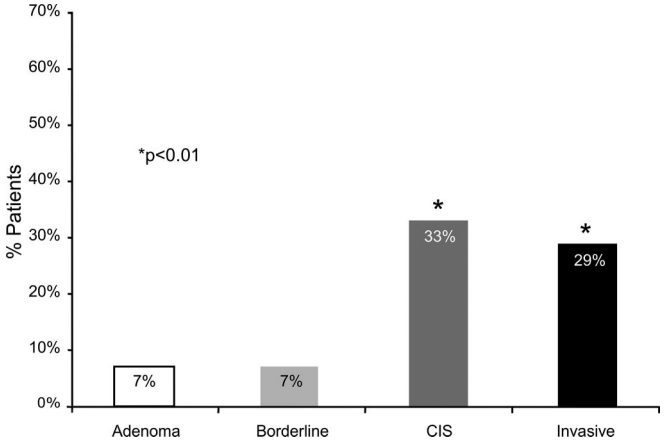

FIGURE 6. Mural nodule incidence in branch-type IPMN according to dysplastic grade (Kruskal-Wallis $*P < 0.01$ for CIS and invasive vs. adenoma and borderline).

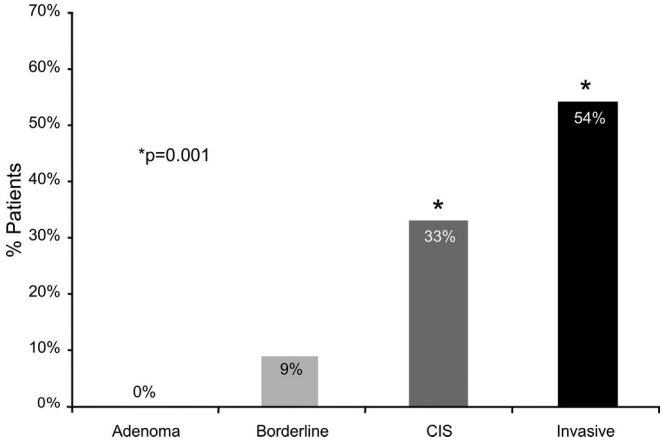

FIGURE 7. Atypical cytopathology incidence in branch-type IPMN according to dysplastic grade (Kruskal-Wallis $*P = 0.001$ for CIS and invasive vs. adenoma and borderline).

In cases of IPMN with *main-duct involvement (main and mixed types combined*), the presence of a mural nodule in IPMN with *main-duct involvement* was predictive of malignant, but not predictive of invasive IPMN ($P = 0.05$, $P = 0.26$, respectively).

Preoperative Cytopathology as It Relates to Malignant or Invasive Pathology

Preoperative cytopathology was performed in 151 (97%) of patients. Atypical cytopathology (atypia) was present in 35 (23%). Patients with malignant or invasive IPMN had cytologic atypia in 25 (52%) and 18 (64%) cases compared with 10 (10%) and 17 (14%) for nonmalignant and noninvasive IPMN. Atypia was a highly significant predictor of malignancy and invasion ($P < 0.001$; $P < 0.001$). Negative predictive value for malignancy and invasion was 80% and 90%, respectively. Positive predictive value for malignancy and invasion was 71% and 64%, respectively. The accuracy of cytopathology in detecting invasive disease was 85%, better than any other diagnostic study.

In *branch-type* IPMN, preoperative cytopathology was performed in 100 (97%) patients. Atypia concerning for malignancy was present in 14 (14%) of branch-type IPMN patients. Patients with malignant or invasive IPMN had cytologic atypia 8 (40%) and 7 (50%) of the time compared with 6 (7%) and 7 (8%) for nonmalignant and noninvasive IPMN. Atypia was a highly significant predictor of malignant and invasive *branch-type* IPMN ($P = 0.007$; $P < 0.001$). Figure 7 shows the significant association of percent of atypical cytopathology according to dysplastic IPMN grade ($P = 0.001$).

In IPMN *with main-duct involvement*, preoperative cytopathology was performed in 51 (96%) of patients. Atypia was a highly significant predictor of malignant and invasive IPMN *with main-duct involvement* ($P = 0.004$; $P = 0.009$).

Multivariate Analysis

Univariate and multivariate analysis of all *preoperative parameters* was performed. Univariate analysis demonstrated male gender, steatorrhea, weight loss, jaundice, number of symptoms, serum CA 19–9, serum alkaline phosphatase, main pancreatic duct diameter, IPMN type, mural nodules, and atypical cytopathology as predictors of malignant of invasive IPMN. Multivariate analysis demonstrated that mural nodule and atypical cytopathology were predictive of malignancy and male gender, mural nodule, and atypical cytopathology were predictive of invasive IPMN (Table 3).

In isolated *branch-type* IPMN, multivariate analysis demonstrated mural nodules and atypical cytopathology as predictors of malignant IPMN and only atypical cytopathology as a predictor of invasive IPMN (Table 3). In IPMN with *main-duct involvement*, multivariate analysis demonstrated

TABLE 3. Multivariate Analysis of All Univariate Predictive Parameters

	Hazard Ratio	*P*
All IPMN		
Malignant		
Mural nodule	6.2	<0.009
Cytopathology	5.9	0.0009
Invasive		
Mural nodule	4.3	<0.04
Male Gender	3.6	<0.002
Cytopathology	6.0	<0.04
Branch IPMN		
Malignant		
Mural nodule	6.9	0.02
Cytopathology	6.4	<0.0006
Invasive		
Cytopathology	8.8	0.004
Main + Mixed IPMN		
Malignant		
Cytopathology	7.2	<0.006
Invasive		
Cytopathology	4.9	0.02

that only atypical cytopathology was predictive of malignant and invasive IPMN (Table 3).

DISCUSSION

In this article, we report a large, single institution retrospective series of predominantly symptomatic patients who underwent surgical treatment for IPMN. The study was designed to determine what radiographic parameters may be used to predict malignant or invasive IPMN pathology. Such parameters would help with relative cancer risk stratification to determine which patients would most benefit from surgical treatment. The study involved an in-depth analysis of all preoperative studies including radiographic imaging and cytopathology. Our study found that IPMN type and MPD size predicts malignant IPMN across all IPMN types, largely reflecting IPMNs with main-duct involvement. The most important finding, however, was that size was not predictive of malignant or invasive IPMN pathology in branch-type IPMN. In branch-type IPMN, the 2 predictors of malignancy and/or invasion on multivariate analysis were the presence of mural nodules or atypical cytopathology consistent with malignancy.

The findings of this study with respect to IPMN involving the main ducts largely reflect the International Consensus Guidelines.[16] The guidelines suggest that patients with a main-duct component to their IPMN (ie, main and mixed types) should be optimally managed with surgical resection. These patients are those predicted by our study to be at the highest risk for malignant and invasive IPMN. Interestingly, in patients with main-duct involvement, the only multivariate factor predictive of malignant or invasive IPMN was atypical cytopathology.

The management of branch-type IPMNs, however, remains controversial. The guidelines suggest that branch-type IPMNs <3 cm can be safely observed if they are asymptomatic and have no concerning radiographic or cytopathologic evidence of malignancy. The guidelines further suggest a management strategy for branch-type IPMNs based on size. For lesions <1 cm in size, management entails serial cross-sectional imaging. For lesions 1 to 3 cm, management entails cross-sectional imaging, endoscopic ultrasound, and cytology. Surgical management is considered for patients with lesions 1 to 3 cm for symptoms or concerning radiographic (eg, mural nodules, main-duct dilation) or cytopathologic evidence of malignancy. For lesions >3 cm, surgical management is recommended even in the absence of other concerning features of malignancy.[16] The findings in our study suggest that size in branch-type IPMN is not related to malignant or invasive IPMN pathology. The size categories <1 cm, 1 to 3 cm, and >3 cm all had a statistically equivalent incidence of malignant and invasive IPMN pathology. A branch-type IPMN <1 cm had an equal likelihood of being malignant as a branch-type IPMN >3 cm. Alternatively, a branch-type IPMN <1 cm has an equal likelihood of being benign as a branch-type IPMN >3 cm.

The International Consensus Guidelines for branch-type IPMN are based, in part, on 2 studies,[10,13] which report a total of 4 branch-type IPMN lesions with invasive pathology all >3 cm. Since the Guidelines were released in 2006, other studies provide evidence that invasive pathology can be detected in lesions <3 cm.[19,21–23] Most series to date, however, do not provide separate analysis of invasive branch-type lesions.[6,9,12–14,16,17] In comparison, our study represents 1 of the largest single institution experiences with invasive branch-type IPMN. The majority of invasive branch-type IPMN in our series were <3 cm (11 of 14).

A limitation of this study is that the series consists largely of symptomatic patients. Thus, we cannot make definitive statements about the management of patients with asymptomatic branch-type IPMN. However, of the 11 asymptomatic cases in this analysis, 3 patients had invasive cancer. One patient had a branch-type lesion (<1 cm) at a second operation for IPMN, and the other 2 had IPMN with main-duct involvement at the primary operation. One of our patients had an asymptomatic branch-type IPMN <1 cm, without concerning radiographic features, which contained microinvasive adenocarcinoma on resection. At least 1 other report of a 1.5 cm invasive branch-type IPMN in an asymptomatic patient without radiographic features concerning for malignancy has been published.[23]

The asymptomatic status of nearly one-third of patients with main-duct involvement who have malignancy has been well documented.[5] Since neither the presence of symptoms nor specific symptoms were predictive of malignant or invasive branch-type IPMN in our study, we would speculate that size of IPMN branch-type lesions in asymptomatic patients does not correlate with malignant or invasive IPMN pathology. However, our patients were also those who underwent surgical resection, which limits the conclusions that can be drawn. Further research must be directed towards patients who are undergoing nonsurgical management of IPMN to determine the true natural history of these lesions and to achieve optimum therapy.

IPMN is a relatively uncommon tumor, and the natural history has not been fully explained.[27] Currently, surgical decision-making must optimize prevention of pancreatic cancer and symptom resolution without subjecting patients unnecessarily to the potential morbidity and mortality of pancreatic surgery. In Figure 8, the incidence of malignant and invasive IPMN at Indiana University is compared with that reported in the literature as documented by the International Consensus Guidelines.[16] For both main and branch-duct lesions, the rates of malignancy and invasion are lower than those reported in the literature.

The management of branch-type IPMN put forth by the International Consensus Guidelines is not supported by our study. The major observation from this series is that small branch-type IPMN has invasive potential, which matches that of larger cysts, and thus, cyst size is not a reliable predictor of malignant or invasive IPMN pathology. Size should be excluded from the International Consensus Guidelines algorithm for the management of branch-type IPMN. If size of branch-type IPMN were removed from the algorithm, all but 1 of our invasive branch-type IPMN patients would have been captured by the remaining International Consensus Guidelines.

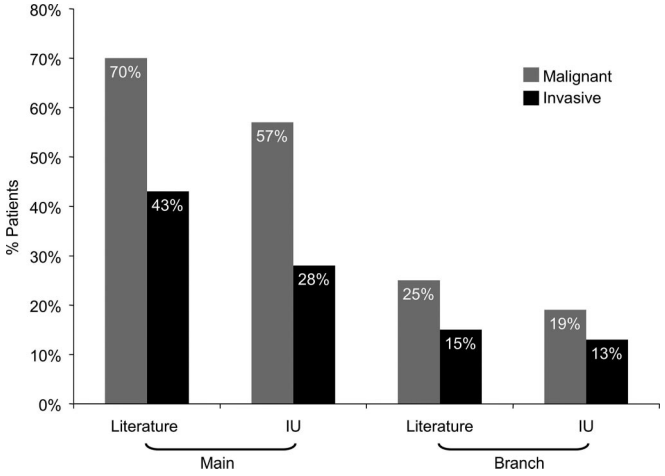

FIGURE 8. Incidence of malignant (gray bars) and invasive (black bars) IPMN in the literature cited in the International Consensus Guidelines and at Indiana University (IU) in main-duct and branch-type lesions.

Multivariate analysis in this study indicates that mural nodularity and atypical cytopathology were predictive of malignancy and/or invasion in branch-type IPMN. The findings from this study should encourage an aggressive work-up including EUS and cytologic sampling of branch-type lesions (even those <1 cm) to detect mural nodularity and rule out malignant transformation. Thus, we recommend that surgery should be undertaken in fit patients with main-duct IPMN and for branch-duct IPMN with mural nodularity or positive cytology irrespective of location, distribution, or size.

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Discussions

DR. CHARLES J. YEO (PHILADELPHIA, PENNSYLVANIA): In this 16-year experience with 150 largely symptomatic patients, Dr. Schmidt and his colleagues provide us with correlates between preoperative radiographic imaging and the endpoints of malignancy. I would caution that "malignancy" is confounded by the inclusion of carcinoma in situ plus invasive lesions, so "malignancy" may not be the endpoint that we want to look at; rather "invasion" is more likely the major endpoint that we care to look at. I have 1 brief comment and 6 quick questions.

My comment: The newest pathology fascicle has modified the older WHO classification and now favors the abandonment of the old terminology, "adenoma, borderline and carcinoma in situ," in favor of low, moderate and high-grade dysplasia, respectively. Many people, including us at Jefferson, have transitioned to this nomenclature because it avoids the confusing borderline status, really reflects the progression from low- to moderate- to high-grade dysplasia, and it further avoids the improper use of the term "malignant" to describe carcinoma in situ, since nobody has ever died of carcinoma in situ of the pancreas.

Question 1: In your manuscript, do you have follow-up data on the 65 patients who have been followed without surgery for presumptive IPMNs? How do you know they truly are IPMNs?

And, as a corollary, what were the criteria to offer resection in these 215 patients? Clearly, in 93% symptoms more than likely were the criteria. But what led you to observe 65 and operate on the other 150?

Question 3: One of the intentions of your study was to use radiologic parameters, which are clearly available preoperatively, to better understand IPMNs. In your data analyses how well do these radiographic criteria correlate with final pathologic findings, in particular lesion size and area, main pancreatic duct diameter, and total number of lesions?

Question 4: IPMNs are increasingly recognized in individuals with familial pancreatic cancer. What percentage of your patients has such a familial link, and do you treat IPMNs in this setting any differently from IPMNs arising in a sporadic setting?

Question 5: The branch-duct lesion findings, that 1 of 7 was invasive, can be interpreted as showing a low but worrisome yield of potentially life-threatening cancer. What do you do at Indiana University with these asymptomatic lesions? Do all patients get EUS and fine needle aspiration? What sort of cytologic assessment is performed? Do you send fluid for cyst CEA? Do you send cyst fluid for molecular markers? I would suspect that most patients who are told they have a 14% risk of harboring an invasive cancer in a branch-duct IPMN would choose to undergo resection.

Lastly, please share with us your algorithm for management of the remnant pancreas after resection. That is, in patients who undergo a partial pancreatectomy, what modality do you use to monitor the remnant pancreas for the development of subsequent metachronous lesions? How many of your 150 patients have undergone re-resection at your mean follow-up of just over 4 years?

Dr. C. Max Schmidt (Indianapolis, Indiana): I will combine the first 2 questions on selection of patients for surgery and follow-up of the 65 patients who were nonsurgical. In general, the criteria for operation in patients with IPMN during this study were main-duct involvement, positive cytology, concerning radiographic features (mural nodularity or mass), symptoms, and size.

Nonsurgical patients fell into 1 of 3 categories: 1) unfit for operation; 2) asymptomatic lesion with no features concerning for malignancy; or 3) the patient preferred a nonsurgical approach. The presumed diagnosis of IPMN in nonsurgical patients was made based on cytology and/or strong clinical suspicion (eg, connection to the pancreatic ductal system, CEA $>$200 ng/ml, multifocality). Our follow-up in these patients is relatively short, so our conclusions are limited. We have had 3 patient deaths to date. One had a main-duct IPMN that developed metastatic pancreatic cancer. The cause of death is unknown in the other 2 patients.

Question 3: This was predominantly a study to examine preoperative predictors of IPMN dysplasia. Surgical pathology is not available preoperatively. Pathologic confirmation of IPMN, the dysplastic stage of IPMN and main-duct involvement were recorded in our study. We did not, however, examine and correlate radiographic lesion size and number with pathologic measurements of the same.

Question 4: We have 3 patient families that I am aware of with familial IPMN/pancreatic cancer. We perform MRI/MRCP annually on the patient family members starting around the age of 35 to 40 years. EUS and FNA biopsy is often performed as a baseline study in patients with radiographic lesions on MRI/MRCP. EUS may also be performed or repeated for change in lesion character (main-duct component). The threshold for operation in these patients is often lower. Some of these patients with radiographically detectable lesions will undergo resection without all the criteria that we normally use for patients that do not have a familial component.

Question 5: As Dr. Yeo pointed out, our series largely represents symptomatic patients, so I think that we really cannot do anything but speculate on what we should do with asymptomatic patients. In main-duct IPMN, Dr. Warshaw's study in conjunction with the Verona group found that there was a high incidence of malignancy in asymptomatic patients. Thus, in main-duct IPMN without symptoms, we feel that fit patients should undergo resection. In terms of the branch-type, I would likewise speculate that absence of symptoms may also not be indicative of benign IPMN in some cases. We approach these patients like patients with symptoms. We will perform MRCP and EUS with FNA biopsy to determine if there are any malignant features such as positive cytology, mural nodules, or a subtle mass not picked up on other imaging studies. We send FNA cells/fluid for cytology and CEA. We have also participated in the PANDA Study looking for ras mutations and are pursuing some novel markers of IPMN dysplasia through our research efforts. Based on all of the information obtained, we calculate an adjusted risk of malignant/invasive IPMN. As the projected percent chance of malignant/invasive IPMN approaches the mortality of the operation, patients prefer observation to surgery.

Question 6: If there is no lesion present after surgery (ie, no index lesion to be followed), we would do MRCP every 6 months to a year. If there is an index lesion (ie, if they had a multifocal type IPMN where only the "most threatening" lesion was removed, based on cytology or other malignant feature), we would also do serial MRCP. In addition, we would do endoscopic ultrasound to examine cytology every 2 years, or more frequently, if there was the development of more concerning findings on MRCP. In terms of patients who underwent re-resection, we had 5 patients who underwent 6 subsequent operations. Half of these were malignant IPMN. Two main-type IPMN recurred and 4 branch-type IPMN developed new lesions. Two of these patients were "apancreatic" as a result of multiple pancreatic resections.

Dr. Andrew L. Warshaw (Boston, Massachusetts): What you said about main-duct IPMNs fits with the consensus at this point; so I am going to confine my comments to the branch-duct IPMNs.

You made some provocative observations, including that branch-duct tumors less than 2 cm contained invasive cancers in 15% versus 14% in tumors greater than 2 cm, that 22% of the invasive branch-duct tumors occurred in the body and tail versus only 10% in the head of the pancreas despite a fairly even distribution overall, and that multifocal tumors also had a lower association with invasion, 20% versus 7%.

The key new and different observation here is that the branch-duct IPMN size seemingly does not correlate with invasion. These findings are in contrast not only to our findings but also to the Consensus guidelines that you have referenced, to which we contributed.

At our institution, of 529 neoplasms resected, 24% were main-duct IPMN and 19% branch-duct IPMN. Of our 145 resected branch-duct IPMN, 46% were benign adenomas, 30% borderline tumors, 11% carcinoma in situ, and 11% invasive cancers. Not different from your numbers overall. But those in the head and uncinate process had a 27% chance of malignancy, while those in the body and tail had only 17% and 14% in multifocal tumors. These numbers are really quite different from your findings.

Similarly, the mean radiologic size, which in our study did not differ significantly from that measured by the pathologist in the resected specimen, was 28 mL in the benign tumors versus 41 mL in the malignant tumors. And that difference was very highly significant.

Although 70% of our tumors were smaller than 3 cm in maximum diameter, there were only 3 invasive cancers in the entire series of branch-duct IPMN under 3 cm. And in our series, as in the Sendai Consensus, the presence of mural nodules and symptoms were strong predictors of malignancy. Nodules occurred in 12 of the 16 invasive tumors and 7 of the 16 carcinomas in situ, but in none of the 66 adenomas.

Our bottom line is that the only 3 invasive cancers in the entire series that were less than 3 cm in diameter all had nodules or symptoms. Whereas 35% of the patients in our series had no symptoms, 93% of the patients in your series did have symptoms. Yours is very different in that respect from most other modern series and likely reflects a significant case selection bias. Our MGH experience, in accord with the International Consensus Guidelines, is that branch-duct IPMNs less than 3 cm are extremely unlikely to contain cancer and can be safely observed unless there are concomitant symptoms or nodules.

My questions are as follows:

Do you think that all of the differences between your series and ours reflect factors other than simply size? Now that more and more of these IPMNs are found incidentally by imaging for other reasons, will your resection criteria evolve from those that led to the present series?

If size does not matter, as you say, what do you do with the multifocal diffuse tumors that may involve the entire pancreas? Do you automatically consider these for total pancreatectomy? We would not think that. We would focus on the dominant cysts that were 3 cm or more.

Dr. C. Max Schmidt (Indianapolis, Indiana): Clearly, based on the Indiana University (IU) series alone, size did not predict malignant or invasive branch-type IPMN. In comparing the IU series to other series, some of the difference may be explained by how size was determined and correlated with IPMN dysplasia. The IU series determined size based on preoperative radiographic imaging and analyzed the relationship of branch-type IPMN size to IPMN dysplasia. Many series include main-type IPMN in the analysis of size and its correlation with dysplasia. In mixing main-type with branch-type IPMN in determination of the correlation of size and dysplasia, we feel that this skews the data.

The other thing to consider, and I think Dr. Warshaw very astutely hinted at this in his questions, is that at IU the mean "lesion size" is 2 cm in the branch lesions. This is significantly smaller than other prominent series. Thus, we may be looking at a selection bias of smaller lesions in this study. Again this small "lesion size", however, may be related to our exclusion of main-duct IPMNs in determination of "lesion size" of branch-type IPMN. Either way, I think it is information that we should digest and incorporate into the management of patients.

Based on this study, we rely less on large branch lesion size to push us towards an operation or on small branch lesion size to dissuade us from an operation. We rely more heavily on cytology, mural nodularity, and main-duct involvement. Our management of multifocal IPMN is similar to yours, however, based on this study, we would resect the "more threatening" lesion not based on size, but rather based on cytology, mural nodularity, and mass or main-duct involve-

ment. One caveat is worth mention: although size does not appear to be a predictor of IPMN dysplasia, it may be a predictor of symptoms simply due to mass effect of the lesion. Thus, there may be non-oncologic reasons for removal of large branch IPMN lesions.

Dr. Murray F. Brennan (New York, New York): Fortunately, most of my questions have been answered. However, if you review the Ong series and the MGH series, there is a 2.5% or 3% risk of malignancy in asymptomatic simple cysts less than 3 cm. So why not resect them all if that is how you feel? Well, it is not a benign operation; you have 2.5% mortality and a 10% total pancreatectomy risk.

So my only comment is that if you have a 2.5% or 3% risk of invasive cancer, the operation begins to approximate the mortality, and that means that 95% of the people suffer the consequences when less than 5% can be corrected. So I do not think size has been dismissed yet. We still have not seen an invasive malignancy under 3 cm without some other feature.

Dr. L. William Traverso (Seattle, Washington): Consensus guidelines are a benchmark to be improved. You have done so with your study, and I rise to thank you. I am not going to ask you any questions, but add only that I am going to go home and look at the patient more than the x-ray.

Dr. John L. Cameron (Baltimore, Maryland): I came away with a different impression from your abstract than from your presentation. From your presentation, I think size does matter. Because there has always been the caveat for the 3 cm branch-duct limit, that a smaller size should be resected if there was a mural nodule, if there were symptoms, if there was positive cytology, or if there were tuberculi, perhaps, in it. And I think most of yours had those modifiers. So the question is if there is a 1 or 2 cm cyst with none of those criteria, no nodules, no trabeauli, negative cytology, asymptomatic, are you going to operate on that patient?

Dr. C. Max Schmidt (Indianapolis, Indiana): No.