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Are Clinical Guidelines for the Management of Intraductal Papillary Mucinous Neoplasms Followed?:

A Single-Center Analysis

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Abstract

Objectives—This study aimed to determine how frequently guidelines for the management of intraductal papillary mucinous neoplasms (IPMNs) are followed and establish factors associated with failure.

Methods—Four hundred forty-five patients with radiographic diagnosis of IPMN 1 cm or greater between January 1, 2003 and January 1, 2013 were included. We defined failure of guideline adherence if the following occurred: (a) failure of acknowledgment of IPMN, (b) failure to undergo endoscopic ultrasound, (c) failure to undergo resection, or (d) failure to undergo at least 1 surveillance image within 2 years after diagnosis.

Results—Failure of guideline adherence was observed in 58% of patients and evident across all the respective criteria (A: 38%, B: 25%, C: 29%, D: 33%). Age older than 68 years ($P < 0.01$), American Society of Anesthesiologists score of 3 or higher ($P < 0.0001$), benign findings on imaging ($P < 0.0001$), and major comorbid conditions ($P < 0.01$) were factors associated with higher rate of failure to compliance. On multivariate logistic regression, American Society of Anesthesiologists score of 3 or higher and benign features were associated with 4.0 times (95% confidence interval, 2.02–8.06) and 2.6 times (95% confidence interval, 1.60–4.07) higher odds of failure to compliance with guidelines, respectively.

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Conclusions—Compliance with clinical guidelines for the management of IPMN is poor. Socioeconomic factors do not seem to create a disparity to care. However, many patients with IPMN have other medical diagnoses that take priority over IPMN surveillance and treatment.

Keywords

intraductal papillary mucinous neoplasms; clinical guidelines; management; socioeconomic disparity

The rise in the routine use of computed tomography (CT) and magnetic resonance imaging (MRI) has led to an increase in the detection of asymptomatic pancreatic cysts.^{1,2} Although as a result, the incidence of intraductal papillary mucinous neoplasms (IPMNs) has increased, our knowledge of this disease entity remains incomplete.^{3–6} It is clear that some IPMNs harbor malignant potential; however, no single feature — such as size alone — has been useful in determining when pancreatic resection should be performed to preempt the development of an invasive pancreatic adenocarcinoma.^{3–10} Once pancreatic cancer has developed, patient outcomes are dismal, underscoring the need for resection criteria that can accurately identify premalignant lesions.^{3,5–8}

Guidelines for the management of patients with IPMNs were first widely established by the Sendai criteria in 2006 and later updated in 2012 with the Fukuoka criteria.^{11,12} The guidelines attempt to address issues including the role of endoscopic ultrasound, fine-needle aspiration, indication for resection, and frequency and duration of follow-up surveillance imaging. These guidelines are notable for their complexity, which make adherence challenging for both physician and patient. More recently, the American Gastroenterological Association (AGA) has released a simplified set of criteria, but validation studies are still lacking.¹³

Despite the presence of established recommendations, it is unclear if these guidelines are routinely followed. The aim of this study was to review our experience with patients diagnosed with IPMN at a single tertiary care center. Our primary end point was to determine how accurately guidelines are followed, which section of the guidelines proved most difficult to complete, and what patient factors are associated with poor adherence. Our secondary end point was to determine if failure to guideline adherence is associated with socioeconomic disparities.

MATERIALS AND METHODS

Institutional review board approval was obtained for this study. The records of all patients with radiographic diagnosis of IPMN between January 2003 and January 2013 at The Mount Sinai Medical Center were reviewed. Patients were identified by a query of the electronic medical record for the ICD9 code for “cyst of the pancreas”, as well as a free-text diagnosis entry of “intraductal papillary mucinous neoplasm” or “IPMN”. A pathology database was also queried to identify all known cases of resected IPMN. Contrast CT/MR images were reviewed by a single radiologist to determine which patients met imaging criteria for diagnosis of IPMN. Imaging criteria was the presence of either a unilocular cyst or clustered

cysts with a demonstrated communication to the pancreatic duct. Cases with cyst size less than 1 cm were eliminated to avoid diagnostic ambiguity.

Summary of Definitions and Guidelines

Our algorithm for the management of patients with IPMN 1 cm or greater is summarized in Figure 1, with major treatment steps identified as A, B, C, and D. The treatment strategies are based on the international consensus guidelines published in 2006 and updated in 2012.^{11,12}

The IPMNs with *worrisome characteristics* included at least one of the following features: cyst size 3 cm or greater, thickened/enhanced cyst wall, nonenhancing mural nodules, main pancreatic duct size of 5 to 9 mm, and abrupt change in duct caliber. The IPMNs with *high-risk characteristics* included at least one of the following features: solid mass, obstructive jaundice, enhanced solid component, and main pancreatic duct size 10 mm or greater.

An endoscopic ultrasound (EUS) was considered indicated in patients with cyst size of 3 cm or greater and/or cysts with worrisome characteristics. Pancreatic resection was considered indicated in patients with high-risk characteristics on radiographic imaging, features suspicious for malignancy on EUS (presence of thickened wall, mural nodule, intraductal mucin, cytology suspicious/positive for malignancy), increase in cyst size of greater than 1 cm/y, and/or suspicious lymphadenopathy. To undergo surgery, patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2 with no significant impairment in cardiac, pulmonary, hepatic, or renal function.

If no resection was indicated, patients were observed with serial imaging per recommendations. Adherence to surveillance guidelines was defined as follows. For cysts sized 1 to 2 cm, we required an annual imaging study (CT or MRI) for at least 2 years from the IPMN diagnosis. For larger cysts (>2 cm), because of the higher level of concern, we required either a repeat EUS at 6 months from diagnosis of IPMN and/or annual CT/MRI.

We defined failure of guideline adherence if at least one of the following occurred: (a) failure of acknowledgment of IPMN by a physician, (b) failure to undergo EUS when indicated, (c) failure to undergo resection when indicated in surgical candidates, and (d) failure to undergo at least 1 surveillance image within 2 years after diagnosis (excluding patients who underwent resection within that time period) (Fig. 1).

Data and Statistical Analysis

Patient demographic and socioeconomic variables included age, self-declared race/ethnicity, language preference, income, insurance type, American Society of Anesthesiologists (ASA) score, cyst characteristics on imaging, EUS characteristics, and surveillance methods, which were recorded. Median annual income was extrapolated from patient ZIP code at the time of hospital admission. Patients with government-supplied insurance were defined as those with Medicare and no supplemental insurance, or those with Medicaid. Low income was defined according to the 2013 US Census Bureau statistics for New York City as median annual household income less than \$35,844, based on the average family size of 2.6 individuals.¹⁴

Continuous variables were presented as mean $\pm$ standard deviation and categorical variables were expressed as valid proportions. Bivariate analyses were performed to assess the relationship between adherence to clinical guidelines and age, sex, race, language, income status, insurance type, ASA score, year of diagnosis, and imaging characteristics. Relationships between adherence and continuous variables were assessed using *t* tests, whereas relationships between adherence and categorical variables were assessed using χ^2 tests and Fisher's exact test when appropriate. Multivariate logistic regression was performed using all variables whose univariate analysis yielded a $P < 0.20$ and other possible confounders as predictors. All analyses were conducted using SAS version 9.3 (SAS, Cary, NC).

RESULTS

During the study period, 1547 patients were identified by data query as having a possible IPMN. Of those, 445 were included in this study based on our radiographic inclusion criteria. The frequency of IPMN diagnosis increased through time from 146 cases in 2003–2007 to 299 cases in 2008–2013. The characteristics of the cohort are summarized in Table 1. The majority of patients were white (58%), men (51%), with ASA scores of 3 or higher (76%), of mid-to-high household income (71%), English speaking (92%), and with governmental insurance status (74%). Of the cohort, 46% had major comorbidities excluding them from surgery.

Failure of guideline adherence was high (58%) and evident across all the decision points (A: 38%, B: 25%, C: 29%, D: 33%) (Table 2). When stricter guidelines were applied to patients with worrisome characteristics (annual imaging studies from diagnosis rather than within 2 years), the rate of noncompliance increased to 73%. Of the 63 patients who underwent resection, 3 were nonindicated according to the guidelines. These had borderline characteristics on imaging with no evidence of malignancy on final pathology.

Age older than 68 years ($P < 0.01$), ASA score of 3 or higher ($P < 0.0001$), benign findings on imaging ($P < 0.0001$), and major comorbid conditions ($P < 0.01$) were factors associated with higher rate of failure to compliance, whereas commercial insurance status ($P < 0.001$) was associated with less failure to compliance in bivariate analyses. Sex, race, income status, and year of diagnosis (2003–2007 vs 2008–2013) were not different among the groups (Table 1), demonstrating the lack of a socioeconomic-related disparity in adherence to guidelines.

Median follow-up time of the entire cohort was 1.9 years (interquartile range [IQR] = 2.7 years/range [0–12 years]). For the group following guidelines, median follow-up time was 2.9 (IQR = 2.3) years versus 1.4 (IQR = 2.6) years for the noncompliant group ($P < 0.0001$).

Multivariate logistic regression demonstrated that ASA score of 3 or higher and benign findings on imaging were the factors associated with 4.0 times (95% confidence interval [CI], 2.02–8.06) and 2.6 times (95% CI, 1.60–4.07) higher odds of compliance failure after adjusting for age, comorbidity, duct dilatation, having symptoms at time of diagnosis, and insurance status (Table 3).

DISCUSSION

Identifying patients with high-risk IPMN is essential to prevent the development of pancreatic adenocarcinoma.^{3–10} To aid clinicians in the management of IPMNs, expert consensus guidelines were drafted at the International Association of Pancreatology (IAP) in 2004. Clinical questions regarding the definition and classifications of cysts, indications for resection, preoperative evaluation, and surveillance methods were answered according to evidence-based literature. These guidelines were then published in 2006 and revised in 2012 and are currently the most widely used practice guidelines for the management of pancreatic cysts.^{11,12}

We report a large cohort of patients diagnosed with IPMN at a single tertiary care center and demonstrate that noncompliance with these guidelines is prevalent, with rates as high as 58%. Noncompliance was demonstrated across all the criteria, with nonacknowledgment of the IPMN diagnosis by the clinicians being the most prevalent. Compliance was irrespective of year of diagnosis (2003–2007 vs 2008–2013) or socioeconomic disparities. Factors associated with noncompliance were patient co-morbidity and the absence of concerning findings on imaging.

We believe that the reason for our finding of poor compliance is multifactorial. First, the guidelines drafted at the IAP were validated by non-American clinicians, and awareness of these guidelines may be limited in the United States. Buscaglia et al¹⁵ published a survey and reported that only 26.2% of EUS specialists and 9.6% of the general gastroenterologists were aware of the practice guidelines set forth by the IAP. However, awareness remains problematic even in the presence of US-based guidelines. Less than half of the responders were aware of IPMN recommendations published by the AGA, American College of Gastroenterology, and American Pancreatic Association, and surprisingly, a significant proportion were unsure whether guidelines existed at all.^{13,15} Furthermore, the guidelines and the multidisciplinary approach required may be too complex, involving multiple steps and therefore making optimal compliance challenging. In fact, the AGA has recently released new IPMN management guidelines, which are significantly simpler than prior iterations with the objective to increase observance rates; however, validation studies are still lacking.¹⁵

Our findings also demonstrate that in circumstances such as the absence of concerning findings on imaging or competing medical priorities, the work-up of IPMN may not be prioritized. Thus, failure to compliance had 2.6- to 4-times higher odds under such conditions. As a large tertiary center, we encounter patients with major comorbidities (76% with ASA = 3) necessitating work-up for other diseases. As the risk of surgery increases in this subgroup of patients and priority is decreased based on other existing health care issues, it may be reasonable to redefine guidelines in this specific cohort.

Lastly, the guidelines remain controversial making adherence challenging. The relative lack of strong evidence-based medicine in the management of IPMN may contribute to the difficulty in clinician decision making.^{15–20} In fact, although the majority felt that surveillance was essential, more than half of the responders disagreed with each guideline

step in the survey published by Buscaglia et al.¹⁵ Differences in agreements persist in terms of the recommended surveillance interval, the method of surveillance, and timing of surgery. 15–20

To our knowledge, this is the largest study reviewing practice trends in the management of IPMN. One of the major strengths of our study was the focus on a large cohort of patients with 1 specific disease, within a single academic center, necessitating a strict management guideline, and where access to advanced diagnostic tools as well as expert gastroenterologist/hepatobiliary surgeons is available. We therefore minimized confounders that may occur with multiinstitutional databases and nonacademic centers where access to care may be limited. In addition, a blinded evaluation was performed by a single radiologist to confirm IPMN features.

Despite these strengths, our study does have some limitations. This is a retrospective analysis and, like any observational studies, may include potential sources of bias. Because the study was performed at a single academic center, the results may not be generalizable to the other regions.

In conclusion, compliance with IPMN guidelines remains poor and seems to be related to the presence of serious comorbidities or competing health care priorities. There do not seem to be any disparities in care based on the measured socioeconomic variables. Future efforts should focus on simplifying guidelines using evidence-based medicine, which may help to increase adherence.

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FIGURE 1.
Guidelines in the management of IPMNs.

TABLE 1

Clinical Data of 445 Patients Diagnosed With IPMN 1 cm or Greater

Variable	Total n (%)	Followed Guidelines (n = 185, 42%)	Failed Guidelines (n = 260, 58%)	P
Age, mean $\pm$ SD, y	66.9 $\pm$ 11.8	64.8 $\pm$ 11.5	68.4 $\pm$ 11.8	0.0012
Sex, male	226 (51)	95 (51)	131 (50)	0.8407
ASA score 3	333 (76)	125 (68)	208 (82)	0.0007
Race				0.3009
White	245 (58)	106 (61)	139 (57)	
Black	56 (13)	19 (11)	37 (15)	
Hispanic	53 (13)	20 (12)	33 (13)	
Asian	34 (8)	18 (10)	16 (7)	
Insurance status				<0.0001
Governmental	326 (74)	124 (67)	202 (78)	
Commercial	102 (23)	58 (31)	44 (17)	
Others	15 (3)	3 (2)	12 (5)	
Annual income, mean $\pm$ SD	\$50,603 $\pm$ \$23,074	\$49,675 $\pm$ \$21,436	\$51,258 $\pm$ \$24,187	0.4965
Low income *	116 (29)	53 (32)	63 (26)	0.2647
English speaking	393 (92)	163 (92)	230 (92)	0.9729
Symptoms				0.0578
None	341 (77)	142 (78)	199 (77)	
Pancreatitis	17 (4)	8 (4)	9 (3)	
Pain	56 (13)	27 (15)	29 (11)	
OBJ/LEF	27 (6)	5 (3)	22 (8)	
Type of study at diagnosis				
CT	170 (38)	70 (38)	100 (38)	0.8938
MRI	275 (62)	115 (62)	160 (62)	
Type of IPMN at diagnosis				0.6922
Main branch	3 (1)	1 (1)	2 (1)	
Side branch	337 (76)	136 (74)	201 (77)	
Mixed	19 (4)	10 (5)	9 (3)	
Unknown	86 (19)	38 (21)	48 (18)	
Multifocal IPMN	171 (38)	70 (38)	101 (39)	0.8294
Largest cyst size at diagnosis (cm), mean $\pm$ SD	18.5 $\pm$ 12.3	19.6 $\pm$ 10.9	17.7 $\pm$ 13.2	0.1139
Location of cyst				0.6323
Head	233 (53)	100 (54)	133 (52)	
Body/tail	209 (47)	85 (46)	124 (48)	
Main pancreatic duct size				0.0647
<5 mm,	408 (93)	167 (92)	241 (93)	
5–9 mm	28 (6)	11 (6)	17 (7)	
10 mm	4 (1)	4 (2)	0	
Major comorbidity (exclusion from surgery)	204 (46)	71 (38)	133 (51)	0.0077

Variable	Total n (%)	Followed Guidelines (n = 185, 42%)	Failed Guidelines (n = 260, 58%)	P
EUS performed	125 (28)	96 (52)	29 (11)	<0.0001
FNA performed	107 (25)	82 (47)	25 (10)	<0.0001
Cyst characteristic				0.0026
Benign	305 (71)	105 (61)	200 (78)	
Nonenhancing mural/enhancing solid component	26 (6)	13 (8)	13 (5)	
Thickened/enhanced wall	8 (2)	4 (2)	4 (2)	
Multiloculated/complex cyst	91 (21)	50 (29)	41 (16)	
Year of diagnosis				0.4489
2007 and prior	146 (33)	57 (31)	89 (34)	
2008 and post	299 (67)	128 (69)	171 (66)	

* Low income defined as income less than \$35,844 (US Census Bureau 2013).

FNA indicates fine-needle aspiration.

TABLE 2

Clinical Data on Guideline Adherence in 445 Patients Diagnosed With IPMN 1 cm or Greater

Variable	n (%)
Failure of acknowledgement when indicated (A)	167 (38)
EUS indicated (14 missing)	167 (39)
Failure of EUS when indicated (B)	42 (25)
Resection indicated (20 missing)	89 (20)
Failure of resection when indicated (C)	26 (29)
Surveillance study <2 y from diagnosis (D)	258 (67)
Yearly surveillance study from diagnosis	121 (31)
Resection within 2 y from diagnosis	57 (13)
Overall nonadherence to guidelines *	260 (58)

* Based on at least 1 surveillance image within 2 years after diagnosis.

TABLE 3

Factors Associated With Failure of Guideline Adherence in 445 Patients With IPMN 1 cm or Greater — Multivariate Analyses

Variable	<u>Multivariate Analysis</u>	
	OR	95% CI
Age	1.410	0.900–2.210
Female	1.049	0.691–1.592
Nonwhite	1.068	0.700–1.628
Commercial insurance	0.729	0.434–1.223
ASA score 3	4.031	2.016–8.061
Diagnosed after 2007	0.950	0.611–1.477
Benign findings on imaging	2.554	1.603–4.069
Major comorbidity	1.116	0.712–1.750
With symptoms	1.309	0.766–2.237
Duct dilatation > 5 mm	1.156	0.506–2.640

OR indicates odds ratio.