Are the Current Guidelines for the Surgical Management of Intraductal Papillary Mucinous Neoplasms of the Pancreas Adequate? A Multi-Institutional Study

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Gregory C Wilson, MD, Shishir K Maithel, MD, FACS, David Bentrem, MD, FACS,
Daniel E Abbott, MD, FACS, Sharon Weber, MD, FACS, Clifford Cho, MD, FACS,
Robert CG Martin, MD, PhD, FACS, Charles R Scoggins, MD, MBA, FACS, Hong Jin Kim, MD, FACS,
Nipun B Merchant, MD, FACS, David A Kooby, MD, FACS, Michael J Edwards, MD, FACS,
Syed A Ahmad, MD, FACS

BACKGROUND: Controversy persists regarding the management of patients with intraductal papillary mucinous neoplasms (IPMN). International consensus guidelines stratify patients into high-risk, worrisome, and low risk categories.

STUDY DESIGN: The medical records of 7 institutions were reviewed for patients who underwent surgical management of IPMN between 2000 and 2015.

RESULTS: There were 324 patients included in the analysis; 60.4% of patients had main-duct/mixed type, and 39.7% had branch-duct IPMN. The median cyst size was 2.65 cm, invasive cancer (IC) or high-grade dysplasia (HGD) was present in 42% (n = 136); 68.9% of patients with high-risk, 40.0% of patients with worrisome, and 24.6% of patients with low risk features exhibited HGD/IC. Multivariate analysis demonstrated that only 1 of 3 high-risk features and 2 of 7 worrisome features predicted the presence of HGD/IC. Positive predictive values for HGD/IC in patients with obstructive jaundice and lymphadenopathy were 0.83 (95% CI 0.65 to 0.94) and 0.69 (95% CI 0.39 to 0.91), respectively. In the absence of high-risk features, HGD/IC was still present in 57.4% of patients with 2 or more worrisome features. Regression analysis demonstrated that each additional worrisome factor present was additive in predicting HGD/IC in a linear fashion (odds ratio 1.39; 95% CI 1.08 to 1.80; p < 0.01).

CONCLUSIONS: These data demonstrate that the current consensus guidelines for surgical resection of IPMN may not adequately stratify and identify patients at risk for having HGD or invasive cancer. Patients with multiple worrisome features, in the absence of high-risk factors, should be considered for resection. (J Am Coll Surg 2017;224:461−469. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant cystic lesions that continue to be diagnosed with increasing frequency, largely due to the widespread use of CT.[1] Given the potentially malignant nature of these lesions, management strategies must balance the risk of malignant progression with the morbidity of surgical resection. Initial consensus guidelines, referred to as the Sendai criteria,

Abbreviations and Acronyms	
EUS	= endoscopic ultrasound
HGD	= high-grade dysplasia
IC	= invasive cancer
IPMN	= intraductal papillary mucinous neoplasm
IQR	= interquartile range
OR	= odds ratio

were proposed during the 11th congress of the International Association of Pancreatology (IAP).[2] Despite these recommendations, a large number of IPMNs that did not meet the Sendai criteria were still found to harbor invasive carcinoma (IC) or high-grade dysplasia (HGD).[3] In order to better risk stratify patients with IPMN, the consensus guidelines were revised at the 14th annual meeting of the IAP in Fukouoka, Japan. These updated guidelines stratified the management of IPMNs based on the presence or absence of high-risk stigmata or worrisome features.[4] These guidelines have quickly become the mainstay on which clinicians rely to assist with clinical decision making in the patient with a newly diagnosed IPMN. These revised guidelines have improved positive and negative predictive values compared with the original Sendai guidelines.[5] Unfortunately, controversy remains over which patients should undergo resections and which patients can be safely observed.

The goal of this study was to evaluate the revised international guidelines for the management of IPMN using a multi-institutional database. Data were collected from all patients undergoing resection for IPMN at 7 academic institutions in order to further study the high-risk stigmata and worrisome features outlined in the current guidelines, and their association with malignancy, in order to further elucidate the optimal management strategy for patients with IPMN.

METHODS
Study population
This retrospective, multi-institutional, observational study includes patients undergoing surgical resection of intraductal papillary mucinous neoplasm of the pancreas. The diagnosis of IPMN was determined by pathologic review in accordance with the established guidelines of the World Health Organization.[6] Tumors with low-grade or moderate dysplasia were considered benign; tumors with HGD or IC were considered malignant. This study population consists of clinical data from the Central Pancreas Consortium, which is a multi-institutional collaboration of 7 academic institutions: University of Cincinnati Medical Center, University of Wisonsin School of Medicine

and Public Health, Northwestern University Feinberg School of Medicine, University of Louisville School of Medicine, University of North Carolina School of Medicine, University of Miami Leonard M Miller School of Medicine, and Emory University Winship Cancer Institute. All patients who underwent pancreatic resection with pathologic confirmed diagnosis of pancreatic IPMN between 2000 and 2015 were included. This study was approved by and conducted in accordance with the standards of each participating institution's IRB.

Patient selection
Indications for surgical resection were determined by each participating institution. In general, all tumors were managed according to international guidelines.[2,4] Before 2012, patients were manged according to the Sendai consensus guidelines. Generally, all main duct and mixed-type IPMNs were resected; branch-duct IPMNs were considered for resection if certain criteria were present including intracystic mural nodule, pancreatic main duct dilation, or cyst size >3 cm.[2] After 2012, institutional algorithms were modified in accordance with the revised internation guidelines.[4] Individual discretion to deviate from the guidelines was left up to the operating surgeon based on clinical evaluation.

Additional work-up included radiographic studies that consisted of contrast-enhanced CT, including pancreatic and portal venous phases, and/or MRI. In select cases, additional diagnostic work-up included endoscopic ultrasound with or without cyst fluid aspiration and biopsy.

Statistical analysis
All statistical analyses were performed using SAS 9.3 and SigmaPlot 11.0 statistical software. A multivariate logistic regression model was performed with all study patients to evaluate the association of high-risk stigmata or worrisome features with IC or HGD. Univariate logistic regression analysis was performed to identify significant factors ($p < 0.05$) for multivariate stepwise logistic regression analysis. A separate logistic regression analysis was performed to evaluate factors associated with IC/HGD in the subset of patients who did not have high-risk stigmata. Patient survival was estimated with Kaplan-Meier log rank analyses. Cutoff values for cyst size and predicting malignancy were evaluated using a receiver operating characteristic curve analysis.

RESULTS
Patient demographics and disease morphology
There were 324 patients from 7 medical centers available for evaluation from 2000 to 2015. Complete demographic