DOI:10.1111/hpb.12305 HPB

ORIGINAL ARTICLE

International Consensus Guidelines parameters for the prediction of malignancy in intraductal papillary mucinous neoplasm are not properly weighted and are not cumulative

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Abstract

Background: The International Consensus Guidelines (ICG) stratify risk for malignancy in patients with intraductal papillary mucinous neoplasm (IPMN) into three progressive categories according to whether patients show 'no criteria', 'worrisome features' (WFs) or 'high-risk stigmata' (HRS).

Objectives: This study was conducted to test the hypothesis that type (clinical versus radiological) and quantity of ICG WFs and HRS carry unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

Methods: A retrospective review of a prospectively maintained database of patients who underwent surgical resection for IPMN at a single, university-based medical centre during 1992–2012 was performed. Differences that achieved a *P*-value of <0.05 were considered significant.

Results: Of 362 patients, 340 were eligible for entry into the study and were categorized as demonstrating no criteria ($n = 70$), WFs ($n = 185$) or HRS ($n = 85$). Patients in the WFs group had higher rates of malignant and invasive IPMN than those in the no-criteria group [26.5% versus 4.3% ($P < 0.0001$) and 15.7% versus 4.3% ($P = 0.02$), respectively]. Patients in the HRS group had higher rates of malignant and invasive IPMN than those in the WFs group [56.5% versus 26.5% ($P = 0.0001$) and 42.4% versus 15.7% ($P = 0.0001$), respectively]. When radiological parameters only were considered for WFs versus HRS, no difference was found in rates of malignant or invasive IPMN. By contrast, when clinical parameters only were considered, patients in the HRS group had higher rates of malignant or invasive IPMN [66.7% versus 8.1% ($P = 0.04$) and 66.7% versus 2.7% ($P = 0.01$), respectively]. There was no stepwise increase in rates of malignant or invasive IPMN with the number of WFs. However, patients with only one WF had a lower risk for malignancy than patients with two or more WFs.

Conclusions: The type and quantity of ICG WFs and HRS carry unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

Received 5 March 2014; accepted 30 May 2014

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) was first described by Ohashi *et al.* in 1982[1] in a series of four mucinous neoplasms of the pancreas with pancreatic ductal ectasia. It was then considered an unusual pancreatic entity. Today, it is believed to account for up to 70% of all cystic neoplasms of the pancreas and is the lead indication for pancreatic resection for pancreatic cystic tumours (10–20% of all pancreatectomies).[2] The reasons for the 'IPMN epidemic' are unknown, but it is likely to reflect increased awareness and better detection with improved imaging

This study was presented at the Annual Meeting of the Americas Hepato-Pancreato-Biliary Association, 19–23 March 2014, Miami, Florida.

resolution. Because of its increased recognition, the World Health Organization (WHO) established criteria in 1996 to classify and distinguish IPMN from other mucin-producing cystic neoplasms.[3] Similarly, physicians, especially surgeons, felt the urge to gather and discuss the management of this rather new entity. In 2006, the working group of the International Association of Pancreatology proposed international consensus guidelines on IPMN (Sendai Consensus Guidelines),[4] which were revised and updated in 2012.[5]

The precancerous nature of IPMN is now widely accepted to imply a sequence of progression to malignancy from low-grade to high-grade dysplasia and finally to invasive carcinoma (comparable with the progression to malignancy of colonic polyps).[6,7] The current International Consensus Guidelines[5] established surgical indications for IPMN based on several surgical series in which rates and predictors of malignancy were analysed according to IPMN histological subtype. With a risk for malignant transformation of 40–95%,[8,9] it is recommended that all main duct (MD) IPMN in fit patients are resected. Conversely, with an overall risk for malignant transformation estimated at 6–40%,[9–11] the close surveillance of branch duct (BD) IPMN seems reasonable except if select criteria are present or appear during follow-up. The Sendai criteria for the management of BD-IPMN[4] were replaced in 2012 by three categories of risk for malignancy according to which patients are stratified as showing 'no criteria', 'worrisome features' (WFs) or 'high-risk stigmata' (HRS).[5] A previous study published by Ohtsuka *et al*. in 2012[12] analysed the Sendai criteria and concluded that an increase in the number of predictive factors augmented the sensitivity for predicting the malignant potential of BD-IPMN. Similarly, the current International Consensus Guidelines,[5] with their three categories of factors, seem to imply that there is a linear relationship between the category and risk for malignancy.

The present authors hypothesized that the type (clinical versus radiological) and quantity of the 2012 International Consensus Guidelines WFs and HRS are of unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

Materials and methods

Patient selection

From 1992 to 2012, data for all patients who underwent surgical pancreatic resection for IPMN at Indiana University Hospital were prospectively collected in a database. For the purpose of this study, this database was retrospectively analysed and supplemented with a review of electronic medical records.

Data were compiled and reported in strict compliance with patient confidentiality guidelines as defined by the Indiana University Institutional Review Board.

Parameters assessed

Based on the 2012 International Consensus Guidelines,[5] a total of nine preoperative parameters were assessed and categorized as representing 'no criteria', 'worrisome features' or 'high-risk stigmata'. The two clinical factors were a history of acute pancreatitis and jaundice. Acute pancreatitis was defined according to the Atlanta consensus or its 2012 revision.[13] Acute pancreatitis was diagnosed if two of the following three features were present: abdominal pain consistent with acute pancreatitis; serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal, and characteristic findings of acute pancreatitis on cross-sectional imaging studies.

The seven remaining factors were radiological and were evaluated on preoperative cross-sectional imaging studies (computed tomography or magnetic resonance imaging/magnetic resonance cholangiopancreatography). They included the size of the largest cyst (<3 cm or ≥3 cm) in BD-IPMN and mixed-type (MT) IPMN, the diameter of the main pancreatic duct (<5 mm, 5–9 mm, ≥10 mm), the presence or absence of an enhancing solid component within the cyst, a non-enhancing mural nodule, thickening enhancing cyst walls or an abrupt change in the calibre of the pancreatic duct with distal pancreatic atrophy and lymphadenopathy.

Pathology

The presence of malignancy as defined by the WHO[14] (high-grade dysplasia, formerly carcinoma *in situ* and invasive carcinoma) and the degree of dysplasia in non-malignant lesions (low-grade and moderate-grade dysplasia) were assessed on final pathology of the surgical specimen. All pathological specimens were reviewed by staff pathologists to confirm the diagnosis of IPMN. Histology was consistent with IPMN if it showed an intraductal proliferation of tall, columnar, mucin-producing cells, arising from the main pancreatic duct and/or a branch duct, with or without papillary projections, and without ovarian-type stroma. Intraductal papillary mucinous neoplasms were also classified into BD-IPMN, MD-IPMN or MT-IPMN based on gross and microscopic histological findings.[5,15,16] For the purpose of the present study, mixed-type variants were considered as MD-IPMN because of the main pancreatic duct involvement.

Exclusion criteria

Patients for whom pathological data were incomplete or whose final pathological diagnosis was not consistent with IPMN were excluded from this study. Patients were also excluded if documentation for all the features described in the 2012 International Consensus Guidelines was not available.

Statistical analysis

Data were recorded using Microsoft Excel 2011 (Microsoft, Inc., Redmond, WA, USA) and analysed with GraphPad Prism Version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics of continuous data included the mean, median, standard error (SE), range and percentage. For subgroup comparisons on categorical data, proportions were compared with Fisher's exact