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Evaluation of the Prognostic Significance of 'High-risk Stigmata' in the International Consensus Guidelines 2012 for Intraductal Papillary Mucinous Neoplasm

Kenjiro Kimura*[,1], Ryosuke Amano[1], Sadaaki Yamazoe[1], Go Ohira[1], Kotaro Miura[1], Kohei Nishio[1], Katsunobu Sakurai[1], Takahiro Toyokawa[1], Bunzo Nakata[2], Akihiro Murata[3], Sadatoshi Shimizu[3], Sayaka Tanaka[4], Masahiko Ohsawa[4], Masaichi Ohira[1] and Kosei Hirakawa

[1]*Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan*
[2]*Department of Surgery, Kashiwara Municipal Hospital, Osaka, Japan*
[3]*Department of Surgery, Osaka City General Hospital, Osaka, Japan*
[4]*Department of Diagnostic Pathology, Osaka City University Graduate School of Medicine, Osaka, Japan*

Abstract

Study Background: In the International Consensus Guidelines 2012 for intraductal papillary mucinous neoplasm (IPMN), 'high-risk stigmata' (HRS) were described as indications for resection. The purpose of this study was to evaluate the prognostic meaning of HRS in the 2012 guidelines.

Method: Clinical and pathological data from 98 patients who underwent pancreatic resection for IPMN at our institution between 1994 and 2014 were retrospectively analyzed.

Results: The 98 resected IPMNs were categorized as demonstrating no criteria (NC) (n=18), worrisome features (WF) (n=39), or HRS (n=46) according to the guidelines. By multivariate analysis, positive lymph node metastasis and HRS were significantly identified as independent prognostic factors. Five-year disease-specific survival rates for NC and WF were both 100%, whereas that for HRS was significantly poorer at 49.5% ($p<0.001$ each).

Conclusions: In this retrospective analysis, HRS were an independent prognostic factor after surgical resection for IPMN. Moreover, HRS offered high diagnostic ability for detecting invasive IPMNs. These results strongly indicated that HRS had high possibility of invasive IPMN and worse prognosis.

Keywords: High-risk stigmata; International Consensus Guidelines 2012; Intraductal papillary

Abbreviations: IPMN: Intraductal Papillary Mucinous Neoplasm; ICG: International Consensus Guidelines; HRS: High-Risk Stigmata; WF: Worrisome Features; NC: No Criteria; CA19-9: Carbohydrate Antigen 19-9; CIS: Carcinoma *in situ*

Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas arises in the main pancreatic duct or its major branches. The papillary epithelium component, degree of mucin secretion, cystic duct dilatation, and invasiveness are variable. The precancerous nature of IPMN is now widely accepted to imply a sequence of progression to malignancy, as with colonic polyps [1,2].

For the management of IPMN, International Consensus Guidelines (ICG) were first published in 2006 [3]. The 2006 ICG were based on expert opinions rather than clinical evidence, due to the limited number of reports available at that time. Subsequent studies have been performed to identify factors predicting malignancy and indications for surgical resection of IPMNs, resulting in the publication of a second set of guidelines in 2012 [4]. In this version, 'high-risk stigmata' (HRS) and 'worrisome features' (WF) were defined to stratify the risk of malignancy. Contrary to the 2006 ICG, which described predictors of malignancy for BD-IPMN only, the 2012 ICG algorithm analyzes all IPMNs altogether, considering main duct dilatation as indicative of WF or HRS.

Many investigators have attempted to identify factors predictive of malignancy and prognostic factors for IPMN. Each of the following have been suggested to be predictive of malignant IPMN: macroscopic type [5,6]; sizes of the tumor [7] and mural nodule [7]; diameter of the main pancreatic duct [8-10]; patulous papilla; cytology of the pancreatic juice; and pathological subtypes [11]. However, no investigations have been conducted on whether WF or HRS represents prognostic factors.

The purpose of this study was to evaluate the prognostic relevance of WF and HRS in the 2012 ICG by analyzing data from 98 consecutive patients with IPMN treated at a single institution.

Materials and Methods

Patients

A total of 98 patients with IPMN who underwent surgical resection at Osaka City University Hospital were included in this study. Informed consent was obtained from all patients to use specimens for this study in accordance with the institutional rules of the hospital. All patients had a confirmed histopathological diagnosis of IPMN of the pancreas based on World Health Organization (WHO) classifications [12]. Clinical records, radiological data, pathological results, and surgical reports in this study were reviewed retrospectively. The median duration of follow-up for all 98 patients was 55 months (range, 5-210 months).

***Corresponding author:** Kenjiro Kimura, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan, Tel. +81-6-6645-3838; Fax: (+81) 6-6646-6450; E-mail: kenjiro@med.osaka-cu.ac.jp

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Definition of radiological type intraductal papillary mucinous neoplasm

IPMNs were classified into three macroscopic types based on preoperative radiological findings. Main duct-type IPMN (MD-IPMN) was defined as showing dilatation of the main pancreatic duct to over 5 mm. Branch duct-type IPMN (BD-IPMN) was defined as showing cystic dilatation of a branch pancreatic duct that communicated with a non-dilated main pancreatic duct. Mixed-type IPMN (MX-IPMN) displayed characteristics of MD- and BD-IPMN. Computed tomography and magnetic resonance cholangiopancreatography were used to determine the radiological type of IPMN, with endoscopic ultrasonography (EUS) added when needed.

Parameters of malignant predictors in the 2012 ICG

Based on the 2012 ICG, a total of nine preoperative clinical and radiological parameters were assessed and cases were then categorized as no criteria (NC), WF, or HRS. HRS was defined as IPMN with at least one of the following factors: obstructive jaundice due to cystic lesion at the head of the pancreas; contrast-enhanced solid component within cyst; or main pancreatic duct ≥ 10 mm. WF was also defined as IPMN with at least one of the following factors: history of acute pancreatitis; cyst diameter ≥ 3 cm; thickened/ enhancing cyst walls; main pancreatic duct size 5-9 mm; non-enhancing mural nodule; or an abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, and lymphadenopathy. Contrary to the 2006 ICG, which described predictors of malignancy for BD-IPMN alone, the 2012 ICG algorithm analyzes all IPMNs together, considering main duct dilatation as indicative of WF or HRS. The present study population thus included BD-IPMNs and MD-/MX-IPMNs both.

Pathology

On the basis of the fourth edition of the WHO classification system, the degree of dysplasia was graded and categorized as low-, intermediate-, or high-grade dysplasia, and IPMN with associated invasive carcinoma [12]. According to the 2012 ICG, low- to high-grade dysplasia was considered as benign, and IPMN with associated invasive carcinomas as malignant. In this study, low- to high-grade dysplasia was classified as 'non-invasive IPMN, and IPMN with associated invasive carcinomas as 'invasive IPMN.

Statistical Analysis

All statistical analyses were performed using JMP statistical software (version 9.0.2; SAS Institute, Cary, NC). The Kaplan-Meier method was used for univariate survival analysis, and log-rank testing was applied. Cox proportional hazard model analysis was used for multivariate survival analysis. Values of $p<0.05$ were considered statistically significant. Variables with values of $p<0.05$ after univariate analysis were used in multivariate analysis.

Results

Patient demographics

The demographic and clinical characteristics of study patients are presented in Table 1. Study subjects comprised 54 men and 44 women with a mean age of 68.3 years at the time of operation. Radiological type was identified as MD-IPMN in 27 cases (27.6%), BD-IPMN in 53 cases (54.1%), and MX-IPMN in 18 cases (18.4%).

In our institute, indications for surgical resection were decided according to ICG 2012, and before publishing ICG 2012 were decided in reference to ICG 2006. Before publishing ICG 2006, surgical indications were not defined clearly and we determined whether doing surgery referring to follows: main pancreatic duct >10 mm, a cyst of greater than 50 mm, solid component within cyst, or the presence of symptom.

The operation performed was pancreaticoduodenectomy in 16 cases (16.3%), pylorus-preserving pancreaticoduodenectomy in 10 cases (10.2%), subtotal stomach-preserving pancreaticoduodenectomy in 17 (17.3%), distal pancreatectomy in 45 (45.9%), total pancreatectomy in 5 (5.1%), central pancreatectomy in 2 (2.0%), and partial resection in 3 (3.1%).

Clinicopathological characteristics

Of the 53 patients with BD-IPMN, 11 cases (20.8%) were invasive IPMN. On the other hand, of the 45 patients with MD-/MX-IPMN, 16 cases (35.6%) were invasive IPMN. No significant differences in malignant ratio were evident between BD-IPMNs and MD-/MX-IPMNs ($p=0.117$).

Histological subtype was gastric type in 36 cases (36.7%), intestinal type in 25 (25.5%), pancreatobiliary type in 34 (34.7%), and oncocystic type in 3 (3.1%).

Based on the 2012 ICG, 18 patients (18.4%) were categorized as showing no criteria (NC), 39 (39.8%) with WF, and 41 (41.9%) with HRS. Among BD-IPMN, 23 cases (51.1%) were categorized as HRS and 17 cases (37.8%) as WF. Among MD-/MX-IPMN, 18 cases (34.0%) were categorized as HRS and 22 cases (41.5%) as WF.

Survival Analysis

Figure 1 shows overall and disease-specific cumulative survival curves. Among all study subjects, 14 patients (14.3%) died of the disease and 9 patients (9.2%) died due to other causes. All disease-related deaths were observed only with invasive IPMN, and no disease-related deaths and disease recurrences were seen in patients with non-invasive IPMN, which included high-grade dysplasia. Cumulative 3- and 5-year overall survival rates were 84.8% and 77.4%, and disease-specific survival rates were 86.0% and 78.5%. Univariate analysis of prognostic factors for IPMN showed mural nodule ($p=0.0042$), lymph node metastasis ($p<0.001$), invasive IPMN ($p<0.001$), HRS ($p<0.001$), and preoperative carbohydrate antigen (CA) 19-9 level ($p = 0.0025$) were significantly associated with prognosis (Table 2).

Multivariate analysis using Cox proportional hazard modeling revealed positive lymph node metastasis (hazard ratio (HR)=0.355, $p=0.037$) and HRS (HR=0.531, $p=0.0018$) as significantly predictive of prognosis (Table 3).

Progression in risk of malignancy across categories

Patients with NC included only two cases of high-grade dysplasia and no cases of invasive IPMNs. Patients with WF included six cases of high-grade dysplasia and two cases of invasive IPMN. On the other hand, patients with HRS included five cases of high-grade dysplasia and 25 cases of invasive IPMN. HRS showed higher rates of invasive lesions than NC (61.0% vs. 0%; $p<0.001$) and WF (61.0% vs. 5.1%; $p<0.001$). HRS showed high diagnostic accuracy for invasive IPMN (81.3%), with 92.3% sensitivity, 77.5% specificity, 61.0% positive predictive value, and 96.5% negative predictive value (Figure 2).

Comparison of disease-specific survival between categories

No patients in either NC or WF groups showed disease recurrence

Total (n = 98)	
Age, mean (SD), y	68.3 (9.0)
Sex ratio (M: F)	54: 44
Location	
Head	44
Body and tail	49
Diffuse/multifocal	5
Radilogical type	
Branch	53
Main	27
Mixed	18
Cyst diameter (mm)	
mean (range)	29.4 (6-110)
Operation	
PD/PpPD/SSPPD	43
DP	45
TP	5
CP/partial resction	5
Dysplasia	
Low grade	33
Intermediate grade	25
High grade (CIS)	13 (11)
IPMN with an associated invasive carcinoma	27

PD: Pancreaticoduodenectomy; PpPD: Pylorus-Preserving Pancreaticoduodenectomy; SSPPD: Subtotal Stomach-Preserving Pancreaticoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy; CP: Central pancreatectomy; CIS: carcinoma in situ

Table 1: Demographic and clinical characteristics of study patients at baseline.

Figure 1

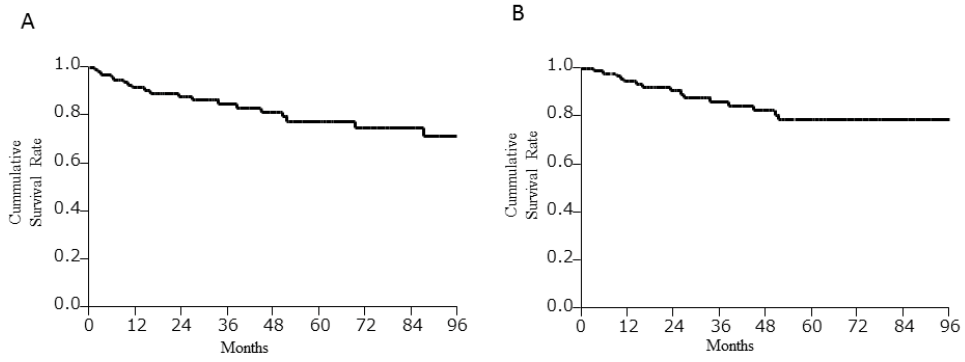

Figure 1: Kaplan-Meier survival curves to show the cumulative survival of patients with intraductal mucinous neoplasms after surgical operation (total n = 98) (A) Overall survival; (B) Disease specific survival.

[5,6,11], we did not find that to be the case. WF and HRS are defined in the 2012 ICG as malignant predictor criteria when deciding indications for resection. A number of studies have investigated the validity of that prediction of malignancy, and all concluded that WF and HRS have high ability in that regard [13-15]. The present study also demonstrates that HRS has a strong ability to predict malignancy. We showed that 61.0% of HRS cases involve invasive IPMN. HRS was thus proven to have high predictive ability for malignancy and high ability to detect for invasive IPMN.

Interestingly, no deaths occurred due to recurrence in the WF and NC groups, resulting in 5-year survival rates of 100%. Conversely, the prognosis with HRS was poor, with a 3-year survival rate of 65.2% and

Factors	n	3-y survival rate	5-y survival rate	*P* value
Sex				0.473
Male	54	0.886	0.729	
Female	44	0.836	0.830	
Radilogical type				0.225
branch	53	0.878	0.848	
main/mixed	45	0.839	0.704	
MPD diameter				0.431
≤5 mm	39	0.869	0.833	
>5 mm	59	0.857	0.748	
Cyst diameter				0.498
≤3 cm	54	0.875	0.840	
>3 cm	44	0.836	0.714	
Mural nodule				0.0042
absent	50	0.944	0.944	
present	48	0.782	0.648	
Lymph node metastasis				<0.001
absent	91	0.938	0.868	
present	8	0.143	0.000	
Invasive IPMN				<0.001
No	71	1.000	1.000	
Yes	27	0.542	0.631	
Histological subtype				0.348
Gstric	36	0.926	0.834	
Intestinal	25	0.790	0.651	
Pancreatobiliary	34	0.869	0.818	
Oncocystic	3	0.500	0.500	
ICG 2012 criteria				<0.001
No criteria	18	1.000	1.000	
Worrisome features	39	1.000	1.000	
High-risk stigmata	41	0.652	0.652	
CA19-9 level (U/mL)				0.0025
≤37	78	0.901	0.853	
>37	20	0.687	0.523	

ICG 2012, the International Consensus Guidelines 2012 of intraductal papillary mucinous neoplasm.

Table 2: Univariate analysis of prognostic fators of IPMNs.

Variable	Comparison	Harzard Ratio	95% CI	*P* value
Mural nodule, present	present vs. absent	0.768	0.488 to 1.209	0.253
Lymph node metastasis, present	present vs. absent	0.355	0.150 to 0.933	0.037
Invasive IPMN	Yes vs. No	1.551	0.803 to 3.86	0.194
ICG 2012 criteria	High-risk stigmata vs.No criteria/Worrisome features	0.531	0.322 to 0.894	0.018
CA19-9 level (U/mL)	>37 vs. ≤37	0.975	0.548 to 1.792	0.932

Table 3: Multivariate Analysis for factors affecting Disease-Specific Survival of IPMNs.

or died of this disease. On the other hand, patients with HRS exhibited poor prognosis, with 3- and 5-year disease-specific survival rates of 65.2% and 49.5%. HRS showed significantly worse prognosis compared with NC or WF (p<.001 each; Figure 3).

Discussion

The present study analyzed the prognostic meaning of HRS in the 2012 ICG. According to our results, HRS represents a prognostic factor after surgical resection for IPMN. Moreover, HRS showed a high diagnostic ability to detect invasive IPMN. To date, prognostic factors for IPMN have been vigorously investigated, but the current study is the first report to identify HRS as an independent prognostic factor for resected IPMN.

The present study population included BD-IPMN and MD-/MX-IPMN both. In our series, the malignant ratio was 20.8% for BD-IPMNs and 35.6% for MD-/MX-IPMN. No significant difference was apparent. In the current study, malignant ratio was lower than several past reports, because we defined only invasive IPMN as malignant. But if malignant IPMN will contain IPMN with CIS (carcinoma *in situ*), malignant ratio of MD-IPMN was 46.7%, and 32.1% in BD-IPMN.

The presence of mural nodule, lymph node metastasis, invasive IPMN, HRS, and high preoperative level of CA19-9 were all significantly associated with poor prognosis in univariate analysis. Moreover, positive lymph node metastasis and HRS independently predicted prognosis on multivariate analysis. Although histological subtype and macroscopic type have previously been reported as prognostic factors

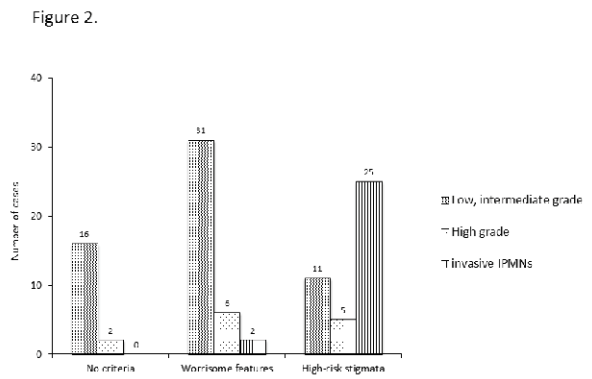

Figure 2: Distributions of the degree of dysplasia according to the categories in the international Consensus Guidelines.

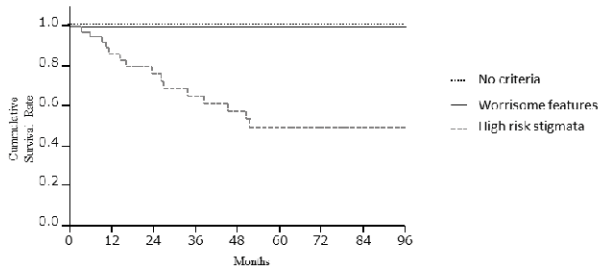

Figure 3: Kaplan-Meier survival curves to show the cumulative survival according to the categories in the international Consensus Guidelines.

a 5-year survival rate of 49.5%. This strongly indicates that we should assume that HRS has high possibility of invasive IPMN and worse prognosis.

The present study has several limitations. First, this was a retrospective study conducted at a single institution. And the sample size was too small to evaluate the validation of the 2012 ICG. Large scale multicenter cohort study is needed to validate the 2012 ICG in the future. Another significant limitation was that the modality for diagnosing each IPMN varied. In particular, EUS was conducted for 75% of cases. EUS is today considered an essential examination for the diagnosis of IPMN, but it is necessary to note that our patient series includes some cases that predated the use of EUS and were diagnosed and underwent surgery without use of this modality.

In conclusion, the present study identified HRS as an independent prognostic factor after surgical resection for IPMN. Moreover, HRS showed a high diagnostic ability to detect invasive IPMN. Our results strongly indicated that HRS had high possibility of invasive IPMN and worse prognosis.

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