Association between the Risk Factors for Pancreatic Ductal Adenocarcinoma and Those for Malignant Intraductal Papillary Mucinous Neoplasm

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Keywords

Intraductal papillary mucinous neoplasm · Pancreatic ductal adenocarcinoma · Smoking history · Risk factors

Abstract

Background and Aims: Risk factors for pancreatic ductal adenocarcinoma (PDAC) include diabetes mellitus, chronic pancreatitis, obesity, a family history of pancreatic cancer, and a history of smoking or alcohol consumption. The aim of this study was to evaluate the association between risk factors for PDAC and malignant intraductal papillary mucinous neoplasm (IPMN). **Methods:** The study included 134 consecutive patients with IPMN who underwent surgical resection at Kindai University Hospital between April 2009 and March 2015. Data on the presence or absence of mural nodules (MNs) and risk factors for PDAC were evaluated.

Multivariable logistic regression analysis was performed with malignant IPMN as the outcome variable and MNs and risk factors for PDAC as explanatory variables. **Results:** The odds ratio of malignant IPMN to MNs was 3.88 (95% confidence interval [CI] 1.53–9.84; $p = 0.004$), whereas that of malignant IPMN to smoking history was 1.66 (95% CI 0.74–3.71; $p = 0.22$). When the presence of MNs was considered as a predictive factor for malignancy, the sensitivity and specificity were 88.5 and 32.1%, respectively, whereas when the presence of both smoking history and MNs was considered, the specificity improved to 73.2%, with a decrease in sensitivity to 42.3%. **Conclusions:** The presence of both a smoking history and MNs was a valuable predictive factor for malignant IPMN with high specificity. A smoking history should be considered before surgical resection in addition to the presence of MNs.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) is diagnosed by several imaging modalities, such as ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and endoscopic ultrasonography. The 2012 international consensus guidelines for the management of IPMN define the presence of mural nodules (MNs) as high-risk stigmata, and IPMN with MN is an indication for surgical resection [1]. Pathologically, IPMN is classified as low, intermediate, or high-grade dysplasia or as invasive [2]. Invasive IPMN at an advanced stage mimics ordinary pancreatic ductal adenocarcinoma (PDAC). Diabetes mellitus (DM), chronic pancreatitis (CP), obesity, a family history of pancreatic cancer, a smoking history, and alcohol consumption are well-known risk factors for PDAC [3–8]. However, the association of these risk factors with malignant IPMN, including high-grade dysplasia and invasive disease, is poorly understood. In this study, we evaluated a database of 134 consecutive patients with IPMN who underwent surgical resection and assessed the association of risk factors for PDAC with malignant IPMN.

Patients and Methods

Study Design

The present study was a single-center retrospective study using prospectively collected data. The final diagnoses were made according to histological specimens obtained during surgical resection. This study was performed with the approval of the ethics committee of Kinki University School of Medicine.

Patients

A total of 134 consecutive patients with IPMN who underwent surgical resection for IPMN at our hospital between April 2009 and March 2015 were included. Patients who underwent surgical resection for PDAC concomitant with IPMN were excluded from the study. Data were collected prospectively before surgical resection and included the presence or absence of MNs, DM (HbA1c [National Glycohemoglobin Standardization Program] ≥ 6.5), CP, obesity (body mass index >30), family history of pancreatic cancer, smoking history (former and current smoker), and alcohol consumption (>37.5 g/day). For DM, information on disease duration and the presence or absence of rapid progression was also collected. For smoking history, pack-years data were also collected.

Definitions

IPMN was classified into main duct type, mixed type, or branch duct type based on imaging studies and according to the 2012 international consensus guidelines [1]. The reference standard was the pathological findings after surgical resection. Malignant IPMN was defined as high-grade dysplasia or invasive disease. Benign IPMN was defined as low- and moderate-grade dysplasia and bor-

Table 1. Patient characteristics ($n = 134$)

Mean age $\pm$ SD, years	69.8 $\pm$ 8.61
Gender, n	
Male	69
Female	65
Location of resected IPMN, n	
Head	94
Body	30
Tail	10
Type of IPMN, n	
Main duct type	19
Mixed type	41
Branch duct type	74
Final diagnosis, n	
Malignant IPMN ^a	78
Benign IPMN ^b	56

SD, standard deviation; IPMN, intraductal papillary mucinous neoplasm. ^a High-grade dysplasia and invasive. ^b Low- and intermediate-grade dysplasia.

derline malignancy. MN was defined as a protrusion of the cyst wall into its lumen that was detected by imaging modalities, such as ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, or endoscopic ultrasonography. Former smokers were defined as patients who had stopped smoking >1 year before surgical resection. Current smokers were defined as patients who were smoking at the time of surgery.

Statistical Analysis

To examine factors affecting malignant IPMN, a multivariable logistic regression analysis was performed in which the outcome variable was malignant IPMN and the explanatory variables were MNs, DM, CP, obesity, family history of pancreatic cancer, smoking history, and alcohol consumption. The sensitivity, specificity, and accuracy for diagnosing malignant IPMN using MNs and/or risk factors for PDAC were calculated. All statistical analyses were performed using JMP software version 13 (SAS Institute, Cary, NC, USA).

Results

The characteristics of the 134 patients are shown in Table 1. According to the pathological classification, the number of malignant and benign IPMNs was 78 (58%) and 56 (42%), respectively. The presence or absence of MNs and/or the risk factors for PDAC in the 134 patients are shown in Table 2. MNs were preoperatively detected in 107 patients and not detected in 27 patients. Table 3 shows the association between the presence or absence of risk factors and malignant or benign IPMN. All patients with CP had malignant IPMN; CP was excluded from the

Table 2. MNs and risk factors for PDAC ($n = 134$)

MN in cyst, n	
Present	107
Absent	27
DM (HbA1c [NGSP] $\geq 6.5\%$), n	
Present	36
Disease duration	
Within 3 years	31
More than 3 years	5
Absent	98
CP, n	
Present	9
Absent	125
Obesity (BMI >30), n	
Present	9
Absent	125
Smoking history, n	
Present	58
Pack-years	
More than 40	32
20–39	25
1–19	1
Absent	76
Alcohol consumption (>37.5 g/day), n	
Present	25
Absent	109
Family history of pancreatic cancer, n	
Present	7
Absent	127

MN, mural nodule; PDAC, pancreatic ductal adenocarcinoma; DM, diabetes mellitus; NGSP, National Glycohemoglobin Standardization Program; CP, chronic pancreatitis; BMI, body mass index.

Table 3. Association between MNs and other risk factors and malignant or benign IPMN

	Benign ($n = 56$)	Malignant ($n = 78$)
MNs, n		
Absent	18	9
Present	38	69
DM, n		
Absent	43	55
Present	13	23
Disease duration		
Within 3 years	1	4
More than 3 years	12	19
CP, n		
Absent	56	69
Present	0	9
Obesity, n		
Absent	52	73
Present	4	5
Smoking, n		
Absent	37	39
Present	19	39
Pack-years		
More than 40	10	22
20–39	8	17
1–19	1	0
Alcohol, n		
Absent	48	61
Present	8	17
Family history, n		
Absent	51	76
Present	5	2

MN, mural nodule; IPMN, intraductal papillary mucinous neoplasm; DM, diabetes mellitus; CP, chronic pancreatitis.

multivariable logistic regression analysis for malignant IPMN despite the strong association of CP with malignant IPMN.

Patients with DM within 3 years of disease duration had high rates of malignant IPMN. Regarding smoking history, the number of pack-years was positively related to the rate of malignant IPMN and the presence of MNs.

Multivariable Logistic Regression Analysis Using Malignant IPMN as an Outcome Variable

The results of the multivariable logistic regression analysis are shown in Table 4. Using a cutoff value of $p = 0.25$, the presence of MNs and smoking history were identified as factors positively associated with malignant

IPMN. Family history was negatively associated with malignant IPMN and was excluded from further analysis.

Sensitivity, Specificity, and Accuracy for Diagnosing Malignant IPMN Using MNs and/or Smoking History

As an additional analysis, we assessed the accuracy of MNs and/or smoking history for the diagnosis of malignant IPMN considering the results of the multivariable logistic regression analysis. When the presence of MNs was considered an indicator of malignancy, the sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy with 95% confidence inter-

Table 4. Multivariable logistic regression analysis of the association between MNs and the risk factors for PDAC and malignant IPMN^a

	Odds ratio	95% CI	<i>p</i> value
<i>Malignant IPMN (outcome variable)</i>			
MN	3.88	1.53–9.84	0.004
DM	1.41	0.58–3.43	0.45
Obesity	0.52	0.12–2.24	0.38
Smoking history	1.66	0.74–3.71	0.22
Alcohol consumption	1.40	0.48–4.05	0.54
Family history of pancreatic cancer	0.22	0.04–1.34	0.10

MN, mural nodule; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; CI, confidence interval; DM, diabetes mellitus. ^a CP was excluded from this analysis because the initial analysis showed that the value of CP was unstable.

vals were 88.5% (82.7–93.2), 32.1% (24.1–38.8), 64.5% (60.3–68.0), 66.7% (49.9–80.4), and 64.9% (58.2–70.5), respectively. The specificity of the diagnosis using only the presence of MNs was low; therefore, we evaluated the diagnostic ability using both MNs and smoking history. Considering both the presence of MNs and a positive smoking history as indicators of malignancy, the sensitivity, specificity, PPV, negative predictive value, and accuracy with 95% confidence intervals were 42.3% (35.4–48.4), 73.2% (63.6–81.7), 68.8% (57.6–78.6), 47.7% (41.4–53.2), and 55.2% (47.2–62.3), respectively.

Discussion

The frequency of high-grade dysplasia or invasive main duct type IPMN is approximately 70% [1, 9]. By contrast, the rate of high-grade dysplasia or invasive branch duct type IPMN is lower; therefore, the indications for the surgical resection of IPMNs, especially for branch duct IPMNs, remain controversial [1, 9]. In this study, we evaluated 134 patients with resected IPMNs and found that 58.2% were malignant. MNs are considered as high-risk stigmata, and 107 of the 134 patients (79.9%) underwent surgical resection because of the presence of MNs; however, the PPV of MNs for malignant IPMN was 64.5%, which was not a satisfactory result. The identification of factors with good predictive value for malignant IPMN is necessary.

Several studies investigated the association of environmental, personal, and hereditary risk factors with the oc-

currence or degree of IPMN [10–14]. Capurso et al. [10] compared 390 patients with IPMN with 390 matched controls and found that a history of DM, CP, and a family history of pancreatic cancer were all independent risk factors for IPMN. Carr et al. [11] examined the association between IPMN malignant progression and smoking in 324 resected IPMNs and found no significant difference in the percentage of invasive IPMNs between smokers and nonsmokers (22 vs. 18%, *p* = 0.5). However, among patients with invasive IPMN, smokers were younger than nonsmokers at the time of diagnosis (65 vs. 72 years, *p* = 0.01). This indicated that smoking might promote IPMN malignant progression. Rezaee et al. [12] reported that patients with main duct type IPMNs were more frequently smokers than patients with mixed and branch duct type IPMNs (*p* = 0.03). However, there was no difference between the 2 groups in terms of the risk of high-grade dysplasia or invasive carcinoma.

The present study showed no significant difference in the incidence of malignant IPMNs between smoking and nonsmoking groups. However, the odds ratio of smoking (1.66) in patients with malignant IPMN was higher than that of environmental, personal, and hereditary risk factors. Moreover, considering a positive smoking history in combination with the presence of MNs as indications for surgery, the PPV and specificity for malignant IPMN increased from 64.5 to 68.8% and from 32.1 to 73.2%, respectively, although the accuracy decreased.

This study had several limitations. The study used a retrospective design and included a small number of patients who underwent surgical resection. The results of the analysis should be validated in a prospective larger study. CP was excluded from the multivariable logistic regression analysis of the association between MNs and the risk factors for PDAC and malignant IPMN because the value of CP was unstable, as all patients with CP had malignant IPMNs. However, CP may be associated with malignant IPMN.

In conclusion, there was no significant association between the risk factors for PDAC and malignant IPMN. The presence of several risk factors, especially a positive smoking history in addition to the presence of MNs, is an indication for surgical resection in patients with IPMN.

Disclosure Statement

There are no potential competing interests concerning this study.

Author Contributions

Ken Kamata: writing of the manuscript, study conception and design, and performing endoscopic ultrasonography. Mamoru Takenaka: writing of the manuscript, drafting conception and design. Atsushi Nakai: data collection. Shunsuke Omoto: data collection. Takeshi Miyata: data collection. Kosuke Minaga: data collection. Tomohiro Matsuda: data collection. Kentaro Yamao: data

collection. Hajime Imai: data collection. Yasutaka Chiba: statistical analysis. Toshiharu Sakurai, Tomohiro Watanabe, and Naoshi Nishida: contribution to writing and revising the manuscript. Takaaki Chikugo: pathological evaluation. Ippei Matsumoto and Yoshifumi Takeyama: surgical resection. Masatoshi Kudo: writing of the manuscript and drafting conception and design. Guarantor of the manuscript: Mamoru Takenaka.

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