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BRIEF ARTICLE

Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms

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Abstract

AIM: To identify preoperative predictive factors associated with malignancy of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas.

METHODS: Between April 1995 and April 2010, 129 patients underwent surgical resection for IPMNs at our institute and had confirmed pathologic diagnoses. The medical records were retrospectively reviewed and immunohistochemical staining for mucin (MUC) in pancreatic tissues was performed.

RESULTS: Univariate analysis showed that the following five variables were closely associated with malignant IPMNs preoperatively: absence of extrapancreatic malignancy; symptoms; tumor size > 4 cm; main pancreatic duct (MPD) size > 7 mm; and lymph node enlargement on preoperative computed tomography (CT). Multivariate analysis revealed that the following two factors were significantly associated with malignant IPMNs preoperatively: MPD size > 7 mm [odds ratio (OR) = 2.50]; and lymph node enlargement on preoperative CT (OR = 3.57). No significant differences in the expression of MUC1, MUC2 and MUC5AC were observed between benign and malignant IPMNs.

CONCLUSION: MPD size > 7 mm and preoperative lymph node enlargement on CT are useful predictive factors associated with malignancy of IPMNs.

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INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae, and cystic dilation of the pancreatic ducts, thus forming

a clinically and macroscopically detectable mass[1]. The classification of IPMNs according to the World Health Organization nomenclature[1] is as follows: adenoma; borderline tumor; carcinoma *in situ* (CIS); and invasive carcinoma. Depending on the degree of dysplasia, treatment of IPMNs includes conservative treatment and radical pancreatectomy with extended resection. Therefore, it is important to diagnose the grade of IPMNs preoperatively.

Previous studies have revealed predictive factors of invasiveness or malignancy of IPMNs of the pancreas[2-8]. Factors, such as age at the time of diagnosis, tumor size, main pancreatic duct (MPD) size, duct type, the presence of mural nodules, the presence of symptoms, and thick septum are associated with invasiveness or malignancy of IPMNs. However, the results of predictive factors have not been consistent with each other and some are not diagnostic. The pre-operative differential diagnosis between benign and malignant IPMNs, or between non-invasive and invasive IPMNs is not easy, despite the development of diagnostic modalities.

Recently, several studies have demonstrated the expression of mucin (MUC) on pancreatic tumors by immunohistochemical staining[9-13]. MUC1 (membrane mucin) is related to the invasive proliferation of tumors, while the expression of MUC2 (intestinal-type secretory mucin) is related to noninvasive proliferation of tumors[14].

The purpose of the current study was to identify preoperative predictive factors associated with malignancy of IPMNs of the pancreas by reviewing patients' records, and to reveal the role of MUC expression in differentiating malignant IPMNs using several specific antibodies.

MATERIALS AND METHODS

Patients and clinical characteristics

Between April 1995 and April 2010, 129 patients who underwent surgical resection for IPMNs of the pancreas at the Samsung Medical Center in Seoul, Korea, and had a confirmed pathological diagnosis were included. The medical records were retrospectively reviewed to obtain the demographic characteristics.

We analyzed variable factors, such as age at the time of diagnosis, sex, presence or absence of diabetes mellitus, alcohol intake history, and cigarette smoking. Symptomatic IPMNs were defined as the presence of abdominal pain and/or jaundice. Recently, IPMNs have been shown to be associated with a high incidence of extrapancreatic gastrointestinal neoplasms[15,16], thus, we assessed preoperatively the presence of extrapancreatic gastrointestinal cancers in the study population.

We determined the serum levels of total bilirubin, amylase, lipase, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19-9 within 1 mo preoperatively. All patients underwent preoperative computed tomography (CT). We assessed the duct type, tumor size, location, MPD size, and presence of mural and intra-abdominal lymph node enlargement on CT. Adenomas and borderline tumors were benign tumors, and CIS and invasive carcinomas were malignant tumors.

Immunohistochemical staining

The surgical specimens were fixed with 10% formalin and cut at intervals of 5 mm. The tumor samples were embedded in paraffin, and the histological sections were cut into 5-μm thick slices for hematoxylin and eosin staining. Immunohistochemical staining for p53, MUC1, MUC2 and MUC5AC was performed on the serial sections for IPMN tissues. The 5-μm thick sections were deparaffinized with xylene, and rehydrated in alcohol. After rinsing in PBS, the sections were incubated for 1 h at room temperature with DF3 (1:50 dilution; Toray-Fuji Bionics, Tokyo, Japan) for MUC1 antigen, Ccp58 (undiluted; Biogenex, San Ramon, CA, USA) for MUC2 antigen, and CLH2 (1:50 dilution; Novocastra, Newcastle, UK) for MUC5AC antigen. In addition, sections were incubated for 25 min at room temperature with BP53.12 (1:400 dilution; Zymed, San Francisco, CA, USA) for p53 antigen. The sections were rinsed with tap water. Positivity of the immunohistochemical stain was judged by the presence of staining in the intraductal tumor cells.

Statistical analysis

Continuous data are presented as the mean ± SD or median and range. The χ^2 test or Fisher's exact test was used to evaluate differences between categorical variables. Significant predictors in the univariate analysis were included in the logistic regression model for multivariate analysis. Differences at $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 17.0k software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

One hundred and twenty-nine patients underwent surgical resection and were confirmed with IPMN of the pancreas (Table 1). The study group included 94 men and 35 women, with a mean age at the time of diagnosis of 60.9 years (range, 32-77 years). More than half of the IPMNs were detected incidentally in asymptomatic patients during routine check-ups. The duct type included the main duct in 56 patients (43.4%), a branch duct in 46 (35.7%), and mixed ducts in 27 (20.9%). Eighty-one of the patients (62.8%) were diagnosed with benign tumors (adenomas and borderline tumors) and 48 (37.8%) had malignant tumors (CIS and invasive carcinomas).

Comparisons of characteristics between benign and malignant IPMNs

There were no differences in age at the time of diagnosis and sex between the patients with benign and malignant IPMNs (Table 2). In both groups, the proportion of current smokers and alcohol drinkers was no different. Of the IPMNs in patients with diabetes mellitus, 37.5% were malignant and 27.1% were benign tumors ($P > 0.05$). Symptomatic IPMNs were observed in 31 of the patients (64.6%) with malignant tumors and 32 (39.5%) with benign tumors ($P = 0.007$). The proportion of patients with tumors > 4 cm in size was greater in patients with malignant IPMNs

Table 1 Demographics and subtypes of intraductal papillary mucinous neoplasms (*n* = 129) (mean ± SD) *n* (%)

Features	Value
Age (yr)	60.9 ± 9.6 (range, 32-77)
Sex (M:F)	94:35
Symptoms	
(-)	66 (51.2)
(+)	63 (48.8)
Mean tumor size (cm)	3.7 ± 3.2 (range, 0.6-16.5)
Mean MPD size (mm)	7.4 ± 4.8 (range, 1.0-30.0)
Tumor location	
Pancreatic head or uncinate process	80 (62.0)
Body or tail	49 (28.0)
Duct types on CT	
Main duct	56 (43.4)
Branch duct	46 (35.7)
Mixed duct	27 (20.9)
Pathologic subtypes	
Adenoma	51 (39.5)
Borderline	30 (23.3)
CIS	5 (3.9)
Invasive	43 (33.3)

MPD: Main pancreatic duct; CT: Computed tomography; CIS: Carcinoma *in situ*.

(37.5%) than benign tumors (18.5%, *P* = 0.019). The MPD was > 7 mm in diameter more frequently in malignant (62.5%) than in benign (33.3%, *P* = 0.002) tumors. According to CT, there were no significant differences in the proportion of patients with mural nodules, the tumor location within the pancreas, and duct types (*P* > 0.05). Intra-abdominal lymphadenopathy, defined as lymph nodes > 1.5 cm in size on preoperative CT, existed in 31.2% of malignant and 9.8% of benign tumors (*P* = 0.003). The mean serum level of amylase in patients with benign IPMNs was higher than in those with malignant tumors (128.0 ± 13.5 U/L *vs* 86.8 ± 61.1 U/L, *P* = 0.173). The mean serum levels of total bilirubin (2.1 ± 4.6 mg/dL), CEA (2.2 ± 1.3 ng/mL), and CA 19-9 (867.9 ± 3958.5 U/mL) in patients with malignant IPMNs was similar to those in patients with benign tumors (0.7 ± 0.4 mg/dL, 6.7 ± 31.9 ng/mL, and 34.5 ± 81.4 U/mL, respectively, *P* > 0.05).

Patients with benign tumors had more extrapancreatic gastrointestinal malignancies before or during the diagnosis of IPMN than patients with malignant tumors (28.1% *vs* 6.2%, *P* = 0.014). Four of 23 patients with IPMNs with extrapancreatic malignancies were women and more than half of all cases were detected at the same time as the diagnosis of IPMN was established. Gastric cancer (10 patients) and lower gastrointestinal tract cancer (eight patients) comprised the majority of extrapancreatic malignancies (Table 3).

Analysis of preoperative findings associated with malignant IPMNs

Univariate analysis showed that the following preoperative variables were closely associated with malignant IPMNs: absence of extrapancreatic malignancy; symptoms; tumor size > 4 cm; MPD size > 7 mm; and lymph node enlarge-

Table 2 Univariate analysis of preoperative findings associated with malignant intraductal papillary mucinous neoplasms of the pancreas

Factor	Benign (*n* = 81)	Malignant (*n* = 48)	*P* value
Age (yr)			
< 60	27	24	0.063
≥ 60	54	24	
Sex			
Male	64	30	0.064
Female	17	18	
Alcohol			
Non-alcoholic	50	37	0.083
Alcoholic	31	11	
Smoking			
Non-smoker	53	35	0.437
Current smoker	28	13	
Diabetes mellitus			
No	59	30	0.242
Yes	22	18	
Symptoms			
No	49	17	0.007
Yes	32	31	
Tumor size (cm)			
≤ 4	66	30	0.019
> 4	15	18	
MPD diameter (mm)			
≤ 7	54	18	0.002
> 7	27	30	
Mural nodules on CT			
No	77	44	0.469
Yes	4	4	
Amylase (U/L)			
≤ 100	53	37	0.173
> 100	28	11	
Total bilirubin (mg/dL)			
≤ 1.2	75	41	0.231
> 1.2	6	7	
CEA (ng/mL)			
≤ 6	79	48	0.529
> 6	2	0	
CA 19-9[1] (U/mL)			
≤ 37	65	32	0.063
> 37	10	12	
Location in pancreas			
Head	52	28	0.575
Body or tail	29	20	
Intra-abdominal lymphadenopathy on CT			
No	73	33	0.003
Yes	8	15	
Duct type			
Main or mixed	47	36	0.059
Branch duct	34	12	
Extrapancreatic malignancy			
No	61	45	0.014
Yes	20	3	

[1]Missing data on CA 19-9 in some patients was presented. MPD: Main pancreatic duct; CT: Computed tomography; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen.

ment on preoperative CT (Table 2). Two of five factors that were significant predictors based on univariate analysis were identified as significant on multivariate analysis: MPD size > 7 mm [odds ratio (OR) = 2.50]; and lymph node enlargement on preoperative CT (OR = 3.57, Table 4).

Table 3 Characteristics of intraductal papillary mucinous neoplasms with extrapancreatic malignancies

No.	Sex	Age (yr)	Diagnosis	Extrapancreatic malignancy	Time of occurrence
1	M	62	Adenoma	Early gastric cancer	Syn
2	M	55	Adenoma	Early gastric cancer	Syn
3	M	66	Adenoma	Colon tubular adenoma	Syn
4	M	58	Borderline	Advanced gastric cancer	Prior
5	F	54	Adenoma	Advanced gastric cancer	Syn
6	F	72	Adenoma	Advanced gastric cancer	Syn
7	F	70	Adenoma	Appendix mucinous tumor	Syn
8	M	64	Adenoma	Colon cancer	Prior
9	M	72	Borderline	Colon cancer	Prior
10	M	56	Invasive	Colon cancer	Syn
11	M	59	Adenoma	Early gastric cancer	Syn
12	M	48	Borderline	Early gastric cancer	Prior
13	M	60	Adenoma	Early gastric cancer	Prior
14	M	67	Adenoma	Early gastric cancer	Syn
15	M	62	Borderline	Early gastric cancer	Syn
16	M	53	Adenoma	Gastric SMT	Prior
17	M	66	CIS	Prostate cancer	Prior
18	M	68	Adenoma	Renal cell carcinoma	Syn
19	M	64	Adenoma	Rectal cancer	Prior
20	M	74	Adenoma	Rectal cancer	Prior
21	M	76	Adenoma	Rectal cancer	Prior
22	F	60	Adenoma	Rectal cancer	Syn
23	M	61	Adenoma	Rectal carcinoid tumor	Syn

SMT: Submucosal tumor; CIS: Carcinoma *in situ*; Prior: Prior to intraductal papillary mucinous neoplasm (IPMN); Syn: Synchronous to IPMN.

Immunohistochemical expression of malignant IPMNs

The expression of pancreatic tissues was present in 22.2%, 29.6%, 96.3% and 11.1% of benign IPMNs for MUC1, MUC2, MUC5AC and p53, respectively (Table 5). In patients with malignant IPMNs, the expression of mucin genes was 17.6%, 57.1%, 94.1%, and 34.5% with immunohistochemical staining for MUC1, MUC2, MUC5A, and p53, respectively. No significant differences in expression of MUCs were observed according to the degree of dysplasia.

DISCUSSION

Several studies regarding the natural course of IPMNs have shown that tumor size < 3 cm, branch duct type, and no mural nodules are low-risk factors of malignancy[17]; thus, the pancreas can be conserved until the tumor progresses to an invasive carcinoma. Therefore, a therapeutic strategy for IPMNs should be based on the stage of the malignancy.

Previous studies that have investigated predictive factors for malignant or invasive IPMNs preoperatively were based on univariate analysis, with only four studies being performed using multivariate analysis[3,5-7]. Our data showed that the presence of extrapancreatic malignancies, symptoms, tumor size > 4 cm, MPD dilatation > 7 mm, and intra-abdominal lymphadenopathy on preoperative CT were significant predictive factors of malignant IPMNs, based on univariate analysis, and only two of the five factors (MPD > 7 mm and intra-abdominal lymphadenopathy on CT) were statistically significant on mul-

Table 4 Multivariate analysis of preoperative findings associated with malignant intraductal papillary mucinous neoplasms

Factors	OR	95% CI	*P* value
Extrapancreatic malignancy - none	3.58	0.95-13.51	0.059
Symptomatic	1.89	0.83-4.32	0.127
Tumor size > 4 cm	2.35	0.96-5.76	0.062
MPD diameter > 7 mm	2.50	1.10-5.65	0.028
Preoperative CT lymphadenopathy	3.57	1.22-10.37	0.020

MPD: Main pancreatic duct; CT: Computed tomography; OR: Odds ratio; CI: Confidence interval.

Table 5 Immunohistochemical staining of intraductal papillary mucinous neoplasms *n* (%)

Markers	Benign IPMN	Malignant IPMN
MUC1	2/9 (22.2)	3/15 (17.6)
MUC2	8/27 (29.6)	8/14 (57.1)
MUC5AC	26/27 (96.3)	16/17 (94.1)
p53	2/18 (11.1)	10/29 (34.5)

IPMN: Intraductal papillary mucinous neoplasm; MUC: Mucin.

tivariate analysis. The present study is believed to be the first to report intra-abdominal lymphadenopathy on CT as a predictive factor, which is not well known for sensitivity and specificity. According to our study, we emphasized the diagnostic importance of CT and recommend it as a follow-up tool to predict malignant changes.

Symptomatic tumors > 3 cm in size are known as important factors for malignancy of branch duct type IPMNs according to international guidelines[18]. In another study[5], the optimal cut-off value for IPMN size in the detection of malignancies was 4 cm. The analysis of our patients divided by tumor size of 3 cm was not statistically significant, thus, we set the cut-off value at 4 cm, which was significantly associated with malignant IPMNs.

A number of previous studies have reported that malignant or invasive IPMNs are more frequently observed in those who have main duct or mixed duct type than branch duct type IPMN[5,18,19]. We showed that the duct type of IPMNs was not affected by malignant transformation of tumors. Patients with the branch duct type in our institute usually underwent wait and watch management, therefore, they were not included with the study group who underwent surgical resection. For the accuracy of predictive factors, follow-up data of branch duct type IPMNs will be necessary in future studies.

The presence of mural nodules has also been reported as a predictive factor of malignant IPMNs[4-7], but it was not associated with malignant tumors in the current study. Mural nodules are usually detected on preoperative multidetector row CT. Mucinous secretions in cystic masses appear to be misdiagnosed as mural nodules because of similarities on CT imaging. Therefore, mural nodules are not diagnostic predictive factors associated with malignant IPMNs.

Our study revealed that benign IPMNs were more likely to have extrapancreatic gastrointestinal malignan-

cies than malignant tumors, which is in agreement with other studies[11,20-22]. The basis for this result has not been explained, but the hypothesis has been advanced that patients with extrapancreatic malignancies were excluded from the study group due to death from underlying cancers[21]. In our study, 28 of 129 patients had an extrapancreatic malignancy and many cases were detected during preoperative evaluation of IPMNs. Gastric or lower gastrointestinal cancers comprised most of the extrapancreatic malignancies, therefore, upper endoscopy and colonoscopy are necessary to detect associations with other gastrointestinal malignancies at the time diagnosis of IPMNs.

IPMN cells secrete a thick MUC that causes dilatation of the MPD. The dysregulation of one or more types of MUCs could lead to formation of malignant IPMNs. There have been several studies[9-14] regarding the expression of MUC in pancreatic tumors. For example, MUC1 is known to be a marker of invasive carcinoma and MUC2 is found only in the intestinal type of IPMNs[10]. In the current study, a difference in the expression of MUC on benign and malignant IPMNs was not demonstrated. Positive staining of MUC1 was shown in 22.2% of adenomas or borderline IPMNs and MUC5AC expression was shown in > 94% of all IPMNs. Cell cycle modulator molecules, for example p53, were similar in both groups.

This study was limited in that it was retrospective and evaluated the predictive factors associated with malignancy, which were diagnosed in most cases by CT. Another limitation was that the examination of MUC expression according to pathological subtypes[23], such as gastric, intestinal, pancreatobiliary, and oncocytic, was not performed, and the study group consisted only of patients who underwent surgical resection. We do not know the significance of patients who received conservative treatment or adjuvant chemoradiation therapy.

In conclusion, a MPD size > 7 mm and preoperative intra-abdominal lymphadenopathy on CT are useful predictive factors associated with malignancy of IPMNs. The proper diagnosis of malignancies in patients with IPMNs is needed for those who are undergoing surgical resection.

COMMENTS

Background
Several investigators have revealed predictive factors of invasiveness of malignancy of intraductal papillary mucinous neoplasm (IPMN), but the results of predictive factors have not been consistent with each other and some are not diagnostic.

Research frontiers
Several recent studies have investigated the role of mucin expression to differentiate the malignancy of IPMN, by using several specific antibodies. Also, it is known that IPMN is associated with a high incidence of extrapancreatic neoplasms.

Applications
It appears to be important to determine the surgical resection of IPMN according to malignant potential.

Terminology
The main pancreatic duct type of IPMNs was treated with surgical resection due to its malignancy, but the branch duct type was sometimes treated without surgery because most tumors of this type of tumor have benign characteristics.

Peer review
This is a good retrospective study. Whether or not the results will prove useful in a prospective fashion is appropriately addressed by the authors.

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