An increase in the number of predictive factors augments the likelihood of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas

Ohtsuka, Takao
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Kono, Hiroshi
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Nagayoshi, Yosuke
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Mori, Yasuhisa
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

他

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Increasing Number of Predictive Factors Augments Likelihood of Malignancy in Branch Duct Intraductal Papillary Mucinous Neoplasm of the Pancreas

Takao Ohtsuka, MD,[a] Hiroshi Kono, MD,[a] Yosuke Nagayoshi, MD,[a]
Yasuhisa Mori, MD,[a] Kosuke Tsutsumi, MD,[a] Yoshihiko Sadakari, MD,[a]
Shunichi Takahata, MD,[a] Katsuya Morimatsu, MD,[b] Shinichi Aishima, MD,[b]
Hisato Igarashi, MD,[c] Tetsuhide Ito, MD,[c] Kosei Ishigami, MD,[d]
Masafumi Nakamura, MD,[a] Kazuhiro Mizumoto, MD,[a] and Masao Tanaka, MD[a]

Departments of Surgery and Oncology,[a] Anatomic Pathology,[b] Medicine and Bioregulatory Science,[c] and Clinical Radiology,[d] Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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All correspondences and reprint requests to:

Masao Tanaka, MD, PhD, FACS

Department of Surgery and Oncology

Graduate School of Medical Sciences, Kyushu University

3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, JAPAN

TEL:+81-92-642-5441, FAX:+81-92-642-5458, E-mail: masaotan@med.kyushu-u.ac.jp

ABSTRACT

Background: International consensus guidelines for the management of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas provide several predictors for malignant IPMNs; however, the sensitivity to predict malignancy of each factor is not so high, and, therefore, it is difficult to determine the appropriate treatment in individual case. The aim of this study was to investigate whether the increasing number of predictive factors might augment sensitivity to detect malignant IPMNs.

Methods: Medical records of 138 IPMNs resected at our institution were reviewed. Possible malignant predictors were analyzed by univariate and multivariate analyses, and then, the effects of number of factors and predictive score on pathological results were examined. The cut-off points of the number of predictors to discriminate malignant IPMNs were sought by constructing receiver operating characteristic (ROC) curves.

Results: Predictive analysis could not be carried out in main duct IPMNs because of the high prevalence of malignancy and too small number of significant predictors. While 4 predictive factors for malignant branch duct IPMNs such as the size of cyst $\geqq$30mm, presence of mural nodule, presence of history of acute pancreatitis, and atypical result of pancreatic juice cytology were determined. Increasing number of those factors significantly affected the sensitivity to predict malignancy. The area under the curve for the number of predictors for malignant branch duct IPMNs was 0.856, and the sensitivity and specificity were 96% and 71%, respectively, when the cut-off point was set at 2. Predictive scoring system also showed the same values of sensitivity and specificity as the number of factors.

Conclusions: Branch duct IPMNs having 2 or more predictors would be the indication for standard pancreatectomy with lymph node dissection, while others with 0 or one

factor could be treated by minimal pancreatectomy without nodal dissection or carefully observed without resection. All main duct IPMNs should be treated by resection as cancers.

INTRODUCTION

Recent intensive investigations for clinical, pathological, and molecular characteristics of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas allow us to understand their biological behavior [1-11]. International consensus guidelines [1] show that all the cases of main duct IPMNs, and branch duct IPMNs with symptoms such as abdominal pain, jaundice, the presence of mural nodule, cyst size ≧ 30mm, and dilation of the main pancreatic duct should be considered for surgical resection because of the possibility of malignancy. However, the sensitivity to predict malignant IPMN of each factor is not so high [2-8], and, therefore, it is difficult to determine the appropriate treatment in individual case; i.e., standard pancreatectomy with lymph node dissection for invasive IPMNs, organ-preserving pancreatectomy for borderline or non-invasive IPMN, and follow-up for benign IPMN. Although several reports have shown the utility of cytology and molecular analyses of the pancreatic juice to evaluate the malignant degree of IPMNs, those assessments are not always consistent with the pathologic results proven after pancreatectomy [12, 13]. Therefore, it is expected to determine some highly sensitive markers to predict malignant IPMNs.

The frequency of malignant IPMNs in main duct type has been reported to range from 60 to 90% [1, 2], and therefore, there might be no way to hesitate the standard pancreatectomy with lymph node dissection for main duct IPMNs. On the other hand, it seems to be difficult to predict the degree of histological grade in branch duct IPMNs according to the criteria of consensus guidelines [1]. We consider that the malignant potential is low in 30 mm of flat branch duct IPMN without any other predictor, while we strongly suspect the cancer in 30 mm of branch duct IPMNs having mural nodule and the presence of atypical cells in pancreatic juice. Therefore, an increase in the

number of predictive factors described above might augment the sensitivity for malignant branch duct IPMNs; however, this kind of analysis has not been employed to date, and consensus guidelines [1] has not also been able to mention about the effects of increasing number of those predictors on the sensitivity for malignancy. The aim of this study was to investigate the relationship between the number of predictive factors for malignant IPMNs and pathologic results.

PATIENTS AND METHODS

Medical records of 161 patients who underwent pancreatectomy for IPMN at the Department of Surgery and Oncology, Kyushu University Hospital between January 1990 and August 2010, were retrospectively reviewed. Fourteen patients having synchronous distinct pancreatic ductal carcinomas and 9 with their pathological results not reported in detail were not included in this study, and thus the data of a total of 138 patients were available. Among them, the data of 126 patients between January 1990 and June 2009 were also used in our previous reports for another objects [14-18]. There were 83 male and 55 female, with the mean age of 67 years (range, 33-85). As the preoperative examinations, contrast-enhanced computed tomography (CT), magnetic resonance imaging / cholangiopancreatography (MRI / MRCP), and percutaneous ultrasonography (US) and/or endoscopic ultrasonography (EUS) were routinely performed. Endoscopic retrograde pancreatography (ERP) and subsequent cytologic examination of the pancreatic juice were also assessed in all patients except for those with difficulty in approach to the duodenal papilla because of the post-gastrectomy state or with a history of sever pancreatitis. We have not performed EUS-guided fine needle aspiration (FNA) cytology to date because of the apprehension of seeding of the tumor cells. Pathologic diagnosis of the IPMN was based on the World Health Organization criteria 2010, i.e., low grade dysplasia (LGD), intermediate grade dysplasia (IGD), high grade dysplasia (HGD) which is compatible for non-invasive carcinoma, and invasive carcinoma [19]. IPMN was classified into 2 types; main duct type and branch duct type based on the preoperative imaging studies as described in our previous reports [14, 15]. Briefly, branch duct type was defined as IPMN exclusively involving branch duct and showing a grapelike collection of small cysts. Main duct type was defined as IPMN

predominantly dilating main pancreatic duct (MPD) without grapelike appearance of branch duct. If the IPMN had grapelike appearance of branch duct with dilation of MPD but did not have findings for main duct involvement such as the presence of mural nodule in MPD, dilated MPD was considered to be caused by mucin hypersecretion from the branch duct IPMN, and thus, such IPMN was classified as branch duct type. Mixed type IPMNs were included in the main duct type in this study.

Based on the international consensus guidelines [1] and previous articles including ours [3-8, 17, 18], 13 preoperative factors possibly predicting malignant IPMNs were estimated. These were gender, age (<65 years / ≧65 years), type (main duct / branch duct), size of cyst in branch duct type (<30mm / ≧30mm), diameter of the MPD in branch duct type (<7mm / ≧7mm), tumor location (pancreas head / pancreas body to tail), presence or absence of mural nodule, symptoms, history of acute pancreatitis, recent deterioration of diabetes mellitus, serum carcinoembryonic antigen (CEA) level (normal limit < 2.3 ng/mL at our institution), serum carbohydrate antigen 19-9 (CA19-9) level (normal limit < 37 ng/mL), and the presence of atypical cells in the pancreatic juice cytology. Presence or absence of mural nodule was judged by US and/or EUS.

The values were expressed as a mean ± standard deviation. Comparisons between the 2 groups were performed by the chi-square test, Fisher's exact probability test, or Mann-Whitney U test. A multivariate logistic regression model was used to determine the effects of possible predictive factors on malignant IPMNs, and then whether the number of these factors would affect the sensitivity to detect the malignant IPMNs was analyzed. Predictive score for malignant IPMN was calculated as the sum of Odds ration of the predictive factor to reflect the importance of each factor, and then the

relationship between the score and the pathologic result was assessed. The optimal cut-off points of the number of predictive factor and the value of predictive score to discriminate malignant IPMNs were sought by constructing receiver operating characteristic (ROC) curves, which were generated by calculating the sensitivities and specificities at several predetermined cut-off points. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

There were 39 main duct and 99 branch duct IPMNs, and pathologically 24 cancer lesions in main duct type (62%) and 22 cancer lesions in branch duct type (22%). The main duct IPMN itself proved to be a significant independent predictive factor for malignancy by univariate ($p<0.01$) and multivariate (95% confidence interval; 1.08-11.10, $p=0.04$) analyses using the data of all 138 patients. In the assessment of 39 main duct IPMNs, the univariate ($p<0.01$) and multivariate (95% confidence interval; 3.58-388.91, $p<0.01$) analyses revealed that only atypical result of pancreatic juice cytology was a significant independent predictor for malignant main duct IPMNs. In terms of the aims of this study to assess the relationship between the number of predictors and malignant IPMNs, further investigation could not be carried out because of the high prevalence of malignancy and too small number of significant predictor in main duct IPMNs.

Table 1 shows the results of univariate analyses of 99 branch duct IPMNs comparing the total number of patients in the non-cancer column with those in the cancer column, and demonstrates that size of cyst ≧30mm ($p=0.02$), presence of mural nodule ($p<0.01$), and atypical result of pancreatic juice cytology ($p<0.01$) were the significant predictive factors for malignant IPMNs. Sensitivity and specificity of pancreatic juice cytology were 54% and 89%, respectively, and there were 11 false positive and 7 false negative findings. Multivariate analysis revealed that presence of mural nodule ($p=0.02$), history of acute pancreatitis ($p<0.01$), and positive pancreatic juice cytology ($p<0.01$) were the significant independent predictive factors for malignant IPMNs (Table 2). Although the statistical value of the size of cyst ≧30mm did not reach to significant by multivariate analysis ($p=0.06$) possibly because this study

population did not include small IPMNs without resection, this factor was included in the further investigation because this is one of the well known predictors for malignant IPMNs [1,2]. Thus, the patient with malignant IPMNs is likely to have some of these 4 factors.

There were 17 patients having no factor in the present series, 39 with one, 29 with 2, 13 with 3 and one with 4 factors, and as a result, the increasing number of those predictive factors significantly affected the sensitivity to predict malignant branch duct IPMNs ($p<0.0001$, Table 3). Most small branch duct IPMNs with zero factor were treated during 1990's decade before the publication of consensus guidelines 2006 [1]. The number of factors in malignant IPMNs was 2.4 ± 0.6, which was significantly greater than that in non-malignant IPMNs (1.1 ± 0.9, $p<0.01$). Detailed histological grade and its relationship with the number of factors are also shown in the right side of Table 3. There was no cancer patient having no factor, and only one patient with one factor (positive pancreatic juice cytology) had HGD (non-invasive cancer). Forty-five % of patients with 2 factors and 54% with 3 factors had cancer lesions including invasive carcinomas. One patient with 4 factors had an invasive IPMN.

Based on the analysis in Table 2, 4 predictive factors had the following respective scores; 5.6 was served for the size of cyst ≧30mm, 5.5 for the presence of mural nodule, 29.8 for the presence of history of acute pancreatitis, and 7.0 for atypical result of pancreatic juice cytology. The predictive score was calculated in each patient, ranging from 0 to 47.9. The mean score of cancer patients was 18.4 ± 10.5 (range, 7 to 47.9), which was significantly greater than that of non-cancer (8.5 ± 8.9; range, 0 to 40.9) ($p<0.01$) (Figure 1A). Figure 1B demonstrates the relationship between the predictive score and detailed histological grade, and shows the stepwise increase in the

value of score according to the degree of histological grade (p=0.01~0.05).

Figure 2A and B the demonstrate ROC curves of the number of predictive factors and the value of predictive score, respectively. The area under the curve (AUC) for the number of factors was 0.856 (95% confidence interval; 0.771-0.918), and the sensitivity and specificity were 96% and 71%, respectively, when the cut-off point to predict malignant branch duct IPMN was set at 2. The AUC for the predictive score for malignant branch duct IPMNs was 0.842 (95% confidence interval; 0.753-0.908), and the sensitivity and specificity were 100% and 66%, respectively, when the cut-off point was set as 7.0. There was no significant difference in AUC between the number of factor and predictive score (p=0.74).

DISCUSSION

Our present study analyzing the relationship between the number of predictive factors for malignant IPMNs and pathological results demonstrated the following findings. (1) Predictive analysis could not be carried out in main duct IPMNs because of the high prevalence of malignancy and too small number of significant predictors.(2) A total of 4 predictive factors for malignant IPMNs such as size of cyst ≧30mm, the presence of mural nodule, presence of history of acute pancreatitis, and the presence of atypical cells in pancreatic juice cytology were determined by univariate and multivariate analyses, and the increasing number of those factors significantly affected the sensitivity to predict malignant branch duct IPMNs. (3) The present scoring system using those 4 predictors also significantly predicted the malignant branch duct IPMNs. (4) The values of the AUC and the sensitivity constructed by ROC curve to predict malignant branch duct IPMNs were high in both systems using the number of factors and the predictive score.

Consistent with our expectation, the present study showed that increasing number of predictive factors affected the sensitivity to predict malignant IPMNs especially in branch duct type. It seems easy to understand that IPMNs with multiple malignant predictors have a high possibility for cancer; however, there has been no report describing the relationship between the number of predictive factors and pathologic results. In addition, we attempted to establish the scoring system using 4 predictors because importance of each factor seems to be different, and our scoring system could predict all the malignant branch duct IPMNs at the cut-off point of 7.0. Fortunately, all 4 predictive factors in the present study are included in factors described in international consensus guidelines [1], and thus, it would be expected to apply these systems to

clinical practice of the management of the branch duct IPMNs.

Based on the results shown in Table 3 and Figure 2A, we can predict 21 of 22 malignant branch duct IPMNs by the use of cut-off point at 2 of the number of predictive factors. On the other hand, one patient with one factor had non-invasive cancer. This factor was the presence of atypical cells in pancreatic juice cytology, and this result reflected the predictive score of 7.0 which was cut-off point for 100% of sensitivity for malignant branch duct IPMNs. And therefore, recommended treatment strategy according to the number of predictive factors would be as follows; branch duct IPMNs without any predictor could be carefully followed-up without resection, those with one factor except for positive pancreatic juice cytology result might be treated by minmal pancreatectomy without lymph node dissection, and those with 2 or more factors should be indication for standard pancreatectomy with lymph node dissection.

Our scoring system could predict all malignant branch duct IPMNs when cut-off point was set at 7.0; however, contrary to our expectation, this scoring system could not further increase the predictive ability, compared with the number of predictive factors. One of the possible reasons might be that the system using the number of predictor has already quite high ability to predict malignant branch duct IPMNs. In the clinical practice, the use of the number of predictors would be easier to be handled compared with the complicated scoring system.

Although both the system using the number of predictors and the scoring system have high sensitivity to predict the malignant branch duct IPMNs, there have been still problems regarding relatively high incidence of false positive findings in these systems. Further investigation should be necessary to diminish the false positive findings. One of the possible ways to resolve this issue might be molecular analysis of pancreatic juice.

Recent reports [10, 11] have demonstrated the several specific markers which can classify the histological grade of IPMNs by the use of resected specimen, and analyses of those markers in pancreatic juice could be applied for the prediction of pathological result. Another way would be the assessment of the cystic fluid obtained by EUS- FNA [20, 21], although this study did not use such samples because of the apprehension of seeding of the tumor cells. Especially in branch duct IPMNs, cystic fluid obtained by EUS-FNA might have more reliable information than pancreatic juice during ERP in terms of the assessment of molecular markers as well as cytology.

Predictive analysis could not be carried out in main duct IPMNs because of the high prevalence of malignancy and too small number of significant predictors. Main duct type seems to be a strong predictor for malignant IPMNs independently, and therefore, all main duct IPMNs should be treated as cancers by standard pancreatectomy with lymph node dissection, as described in the consensus guidelines [1].

Preoperative imaging study is principal to predict the malignant potential of IPMNs, and, one of the limitations of the present study is to include the patients who underwent operation 20 years ago because the imaging studies have changed during recent 20 years dramatically [2]. In addition to the assessment of cystic size and the presence of mural nodule, recent imaging studies have given us more detailed information to predict the malignant potential of IPMNs. We recently showed that positive radiologic findings for invasive IPMNs are the good predictor for lymph node metastasis [17]. Other group classified the mural nodules of IPMNs into 4 morphologic types based on the findings of EUS and showed that type III (papillary nodule) and IV (invasive nodule) were associated with invasive carcinomas [22]. We might be able to determine the more reliable imaging factors to predict malignant IPMNs in the future.

The other limitation seems to be the selection bias of the study population. Because many small branch duct IPMNs without any predictors which had been carefully observed without operation were not included in this series. Most of them should be benign, although it is quite difficult to confirm the pathology in patients without resection of small branch duct IPMNs. On the other hand, there might be the possibility that several potential malignancies were missed because they were not selected for surgery. We previously demonstrated the surveillance data of 93 small branch duct IPMNs without resection, and showed that there was no patients having rapid progression of the diseases requiring the resection during mean follow-up period of 31.6 moths [14]. Although this study population included only 17 patients without any predictor, all of them had non-cancer lesions. Thus, the branch duct IPMNs without any predictor could be carefully observed without resection.

In conclusion, increasing number of predictive factors would augment sensitivity to detect malignant branch duct IPMNs. Branch duct IPMNs without any predictor could be carefully followed-up without resection .Those with one factor except for positive pancreatic juice cytology result might be treated by organ-preserving pancreatectomy without lymph node dissection, and those with 2 or more factors should be indication for standard pancreatectomy with lymph node dissection. All main duct IPMNs should be treated by resection as cancers.

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249: 628-634.

FIGURE LEGENDS

Figure 1. Relationship between the predictive score and pathological results of branch duct IPMNs.

(A) Predictive score of cancer lesions is significantly higher than that of non-cancer lesions. (B) Predictive score shows stepwise increase according to the histological grade. LGD; low grade dysplasia, IGD; intermediate grade dysplasia, HGD; high grade dysplasia.

Figure 2. Receiver operating characteristic (ROC) curves of the number of factors and the predictive score in branch duct IPMNs.

(A) The area under the curve (AUC) for the number of factors is 0.856, and the sensitivity and specificity are 96% and 71%, respectively, when the cut-off point to predict malignant IPMN is set at 2. (B) The AUC for the predictive score for malignant IPMNs is 0.842, and the sensitivity and specificity are 100% and 66%, respectively, when the cut-off point is set as 7.0. There is no significant difference in AUC between the number of factor and predictive score.

Table 1. Univariate analysis of preoperative factors predictive of cancer in 99 branch duct IPMNs.

	Non-Cancer (n=77)	Cancer (n=22)	p-value
Gender (male / female)	44 / 33	16 / 6	0.19
Age(years) (<65 years / ≧65 years)	33 / 44	8 / 14	0.63
Size of cyst (< 30mm / ≧ 30mm)	31 / 46	3 / 19	0.02
Diameter of main pancreatic duct (< 7mm / ≧ 7mm)	31 / 46	8 / 14	0.79
Location (pancreas head / pancreas body to tail)	49 / 28	16 / 6	0.61
Mural nodule (yes / no)	25 /52	16 / 6	< 0.01
Symptoms (yes / no)	29 / 48	9 / 13	0.81
History of acute pancreatitis (yes / no)	6 / 71	4 /18	0.15
Recent deterioration of diabetes mellitus (yes / no)	0 / 77	2 / 20	0.47
Serum CEA level (normal / high)*	63 / 12	16 / 4	0.74
Serum CA19-9 level (normal / high)**	70 / 7	19 / 3	0.69
Pancreatic juice cytology (benign / atypical)***	59 / 11	7 / 13	< 0.01

*Carcinoembryonic antigen (CEA) was assessed in 95 patients. **Carbohydrate antigen 19-9 (CA19-9) was assessed in all 99 patients.
***Pancreatic juice cytology was assessed in 90 patients.

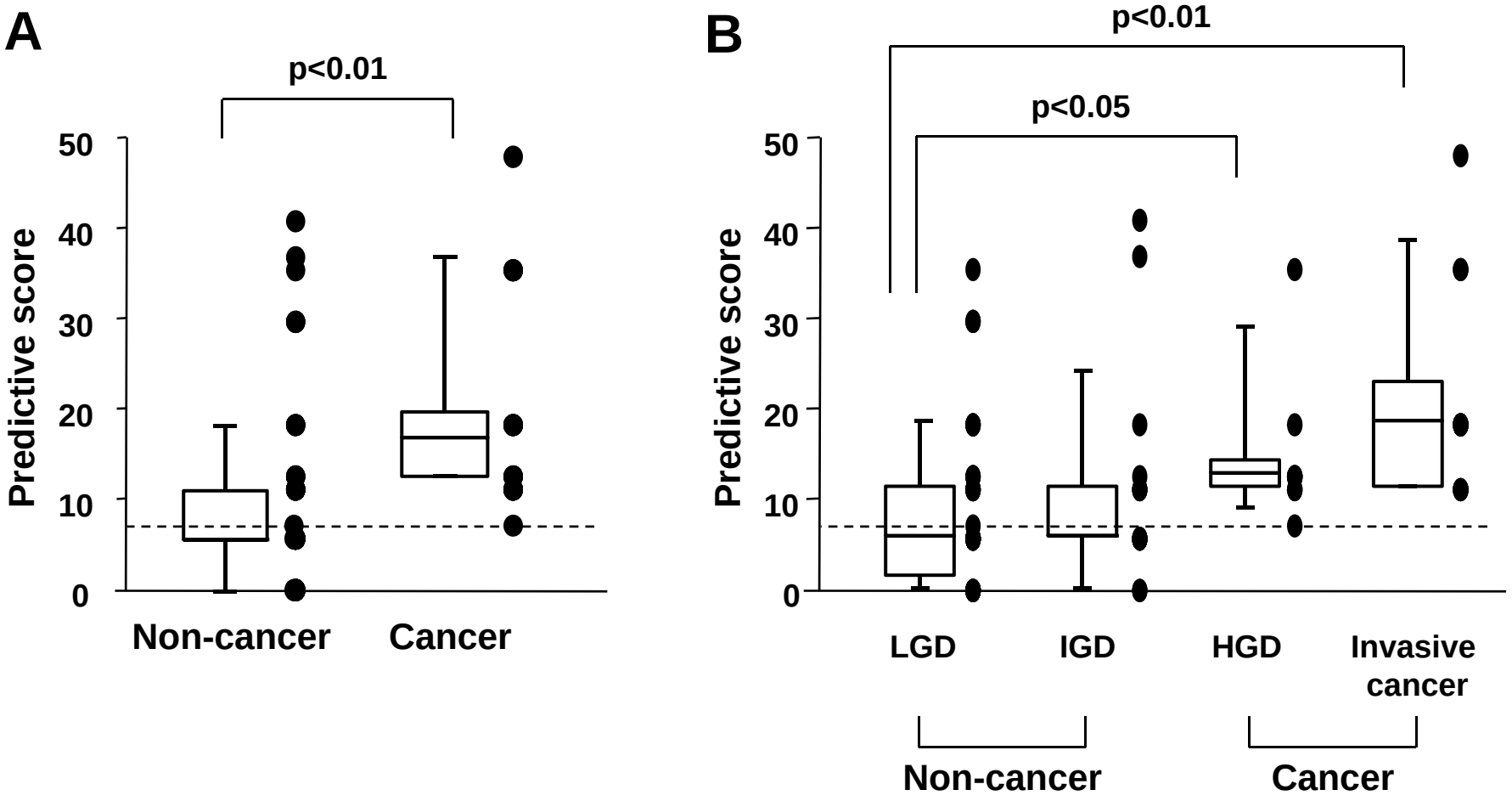
Table 2. Multivariate analysis of preoperative factors predictive of cancer in 99 branch duct IPMNs.

	95% interval	Odds ratio	p-value
Gender, male	0.36 - 7.13	1.6	0.54
Cyst size, ≧30mm	0.86 - 35.93	5.6	0.06
Mural nodule, yes	1.37 - 22.06	5.5	0.02
History of acute pancreatitis, yes	2.99 - 297.27	29.8	<0.01
Recent deterioration of diabetes mellitus, yes	-	219756	0.98
Pancreatic juice cytology, atypical	1.84 - 26.90	7.0	<0.01

Table 3. Relationship between number of factors and pathologic results in 99 branch duct IPMNs.

Number of factors	Non-cancer	Cancer	Total	Sensitivity for cancer	Pathologic grade			
					Non-cancer		Cancer	
					Low grade dysplasia	Intermediate grade dysplasia	High grade dysplasia	Invasive cancer
0	17	0	17	0	14	3	0	0
1	38	1	39	3%	27	11	1	0
2	16	13	29	45%	10	6	7	6
3	6	7	13	54%	4	2	1	6
4	0	1	1	100%	0	0	0	1
Total	77	22	99		55	22	9	13

Figure 1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Non-cancer
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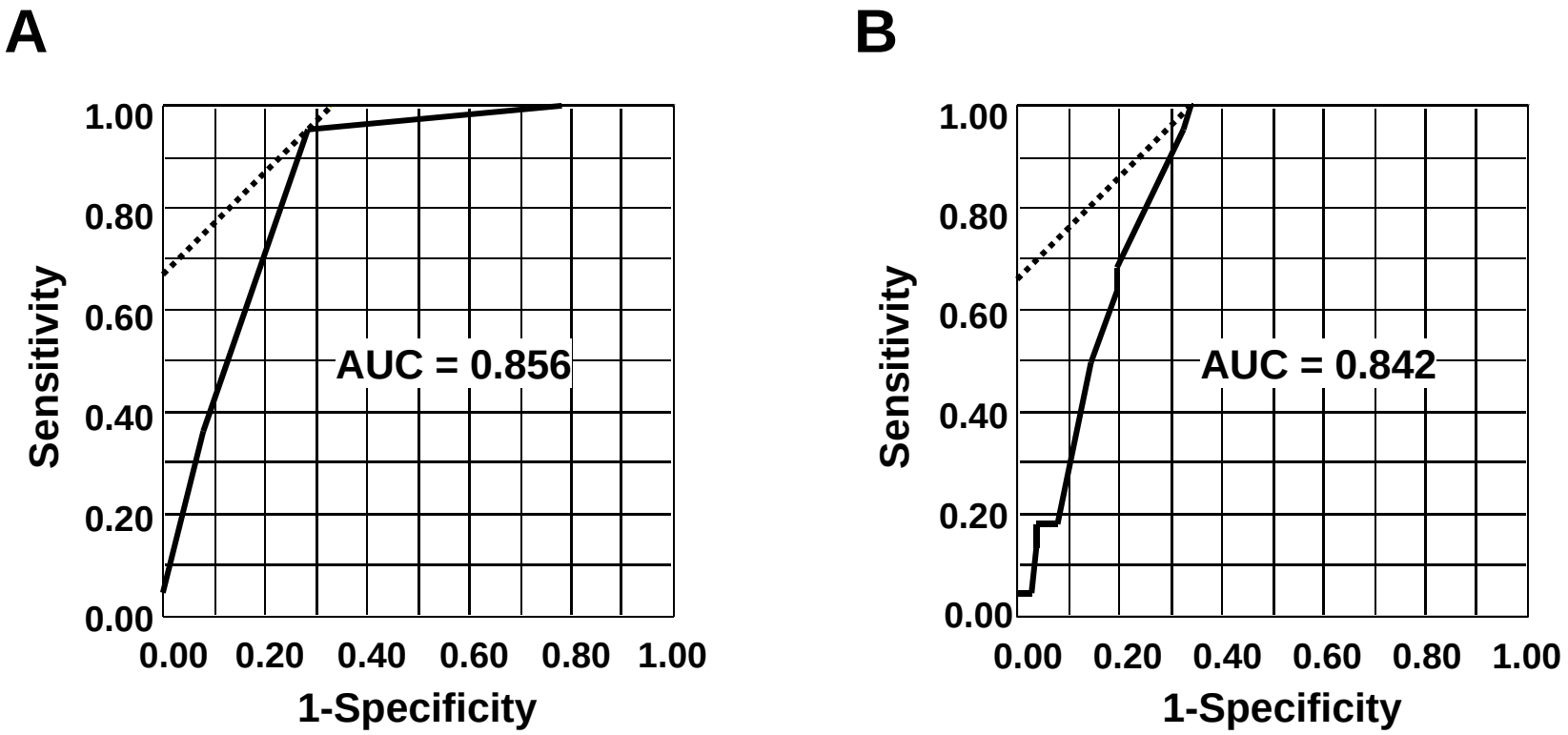
LGD
IGD
HGD
Invasive cancer
Non-cancer
Cancer

Figure 2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