The Korean Journal of Pathology 2010; 44: 410-9
DOI: 10.4132/KoreanJPathol.2010.44.4.410

Clinical Outcome of Surgically Resected Pancreatic Intraductal Papillary Mucinous Neoplasm According to the Marginal Status: A Single Center Experience

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Received : November 23, 2009
Accepted : April 12, 2010

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*This study was supported by a grant (2010-483) from the Asan Institute for Life Sciences, Seoul, Korea.

Background : Surgical resection is the treatment of choice of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. However, the benefit of clearing resection margin is still controversial. **Methods :** We reviewed 281 surgically resected cases of IPMN. The recurrences were compared according to the histologic grade (benign or borderline IPMN, malignant noninvasive IPMN, invasive carcinoma) and size (pancreatic intraepithelial neoplasia, PanIN, less than 0.5 cm in the long axis; and IPMN, greater than or equal to 0.5 cm) of the residual lesions at the resection margin. **Results :** Sixty cases (21.4%) were invasive carcinoma, and 221 (78.6%) noninvasive cases included 87 (31.0%) benign, 107 (38.1%) borderline and 11 (3.9%) malignant noninvasive IPMN cases. In noninvasive IPMN, increased recurrence in patients with five or more years of follow-up was only related to the involvement of resection margin by severe dysplasia. The recurrence of invasive carcinoma was high (27.3%) even when the resection margin was clear, and was not related to the grade or size of residual tumors at the resection margin. **Conclusions :** Invasiveness is a strong risk factor for recurrence in IPMN regardless of the status of the resection margin. However, in noninvasive IPMN, histologic grading of residual lesions at the resection margin predicts local recurrence.

Key Words : Pancreas; Neoplasms, mucinous; Carcinoma, intraductal, noninfiltrating; Recurrence

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a neoplasm of the pancreatic duct epithelium characterized by intraductal papillary growth and mucin secretion.[1] The degree of dysplasia ranges from benign, to frankly malignant[1] and the epithelial type can be classified into four categories according to distinctive architecture and histochemical features: gastric, intestinal, pancreatobiliary and oncocytic type.[2-5] IPMN involves the main pancreatic duct or its major branches, and therefore is usually visible grossly or by radiographic imaging. In addition to IPMN, abnormal epithelial proliferation can also occur as pancreatic intraepithelial neoplasia (PanIN). In contrast to IPMN, however, PanIN involves the smaller caliber ducts and is generally too small to be seen grossly or by radiographic imaging.[6]

Complete surgical resection is the treatment of choice for IPMN because it gives the best cure rate with acceptably low operation-related mortality or morbidity[7-9] and because there is no other reliable tool to investigate the invasiveness of IPMN, properly.[9-11] However, it has not been clearly determined how complete the resection should be and whether the remaining pancreas should be resected further when the resection margin is involved by noninvasive IPMN.[3,7,9,12] Furthermore, the influence of PanIN at the resection margin on tumor recurrence has not been fully evaluated yet. Because it is difficult to accurately delineate the extent of involvement of the pancreas by IPMN preoperatively, the intraoperative evaluation of resection margin is mandatory.[7,11] Therefore, it would be very helpful to both surgeons and pathologists to know the true benefit of further excision and the risk of recurrence when the pancreatic resection margin contains PanIN or noninvasive IPMN.

There is also controversy about the management of positive resection margins during the resection of invasive carcinoma arising in IPMN because of the frequent recurrence and poor prognosis.[9,13-15] Doubts have been raised about the clinical ben-

efit of extended or total pancreatectomy (sacrificing exocrine and endocrine function) after incomplete initial resection, as assessed by intraoperative evaluation of the resection margin.[3,7,9,13]

To resolve the problem, we analyzed the clinicopathologic characteristics and long-term outcome of patients with IPMNs resected at our institution. To investigate the clinical consequence of positive resection margin further, we described the histologic features of the lesions involving resection margins in detail, according to grade of dysplasia and the size of the lesion (PanIN, lesions < 0.5 cm vs IPMN, lesions ≥ 0.5 cm) and correlated them with the disease recurrence. Because IPMNs usually grow slowly and can recur late in the disease course,[13] a sufficient follow-up period is needed to investigate the true risk of recurrence, especially in noninvasive IPMNs. Consequently, in the case of noninvasive IPMN, we separately analyzed cases with five or more years of follow-up to evaluate the association between resection margin status and long-term risk of recurrence.

MATERIALS AND METHODS

Examination of clinicopathologic features

We reviewed the clinicopathologic data of 281 consecutive IPMN resection cases between May 1996 and May 2008 at Asan Medical Center. Of the 281 IPMN cases, 118 cases have already been described by the department of surgery in our institution.[14] The median follow-up period was 3.8 years (range, 4 months to 13.2 years). The patients consisted of 181 men and 100 women (male : female = 1.81 : 1) with a median age of 63 years (range, 34 to 82 years).

The diagnosis of IPMN was confirmed histologically by two experienced pathologists. According to the topography of involved ducts, main duct-type IPMN (Fig. 1A) was designated when the tumors involved the main pancreatic duct regardless of the involvement of branch ducts. Therefore, mixed main and branch duct IPMNs were categorized as main duct-type and the tumors confined only to the branch ducts were classified as branch duct-type IPMN (Fig. 1B). Regarding the degree of dysplasia, tumors were classified into four categories according to World Health Organization classifications (Fig. 2): benign IPMN, borderline IPMN, malignant noninvasive IPMN and invasive carcinoma. The first three categories were defined as noninvasive IPMNs. When various degrees of epithelial dysplasia coexisted, the tumors were categorized according to the most severe degree of dysplasia observed. Epithelial types were determined by the morphologic features of epithelial cells and papillary structures with reference to the consensus study by Furukawa *et al*.[4] Among the four subtypes described, there were three subtypes: gastric, intestinal and pancreatobiliary types. Oncocytic type was not included in our series. Briefly, the gastric-type IPMNs (Fig. 3A) consisted of cells resembling gastric foveolar epithelium which showed basally located nuclei and covered thick finger-like papillae. The intestinal-type IPMNs (Fig. 3B) resembled intestinal villous neoplasm, which is characterized by elongated oval nuclei and pseudostratification. The pancreatobiliary-type IPMNs consisted of cells resembling cholangiopapillary neoplasms and showed thin, branching, complex papillae (Fig. 3C, D).

The term "pancreatic intraepithelial neoplasia (PanIN)" was

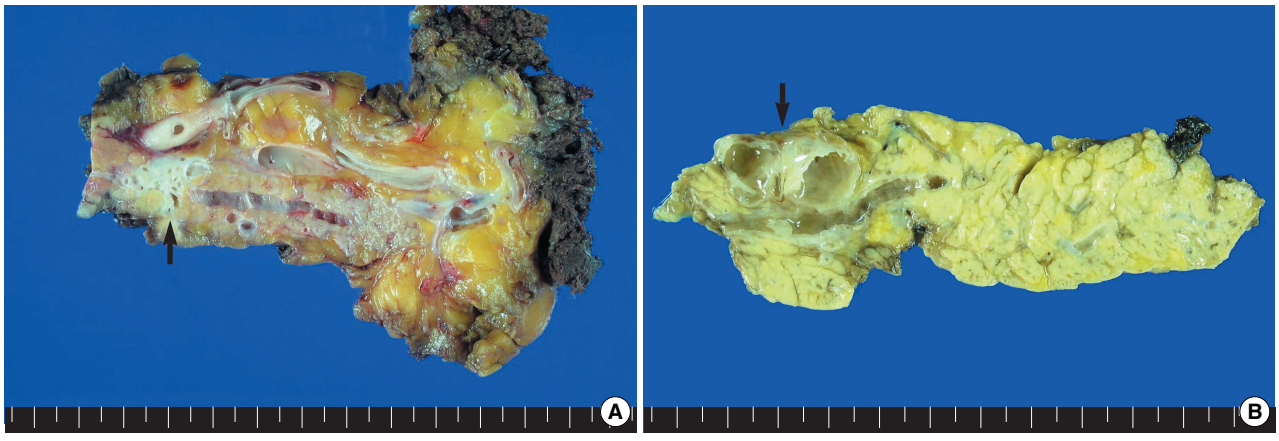

Fig. 1. Gross photographs of pancreatectomy specimens. (A) Main duct type malignant intraductal papillary mucinous neoplasm (IPMN). Infiltrative mass is in the main pancreatic duct with dilatation of the proximal ducts. (B) Branch duct type borderline IPMN. Multilocular cystic lesion is located beside the dilated main pancreatic duct.

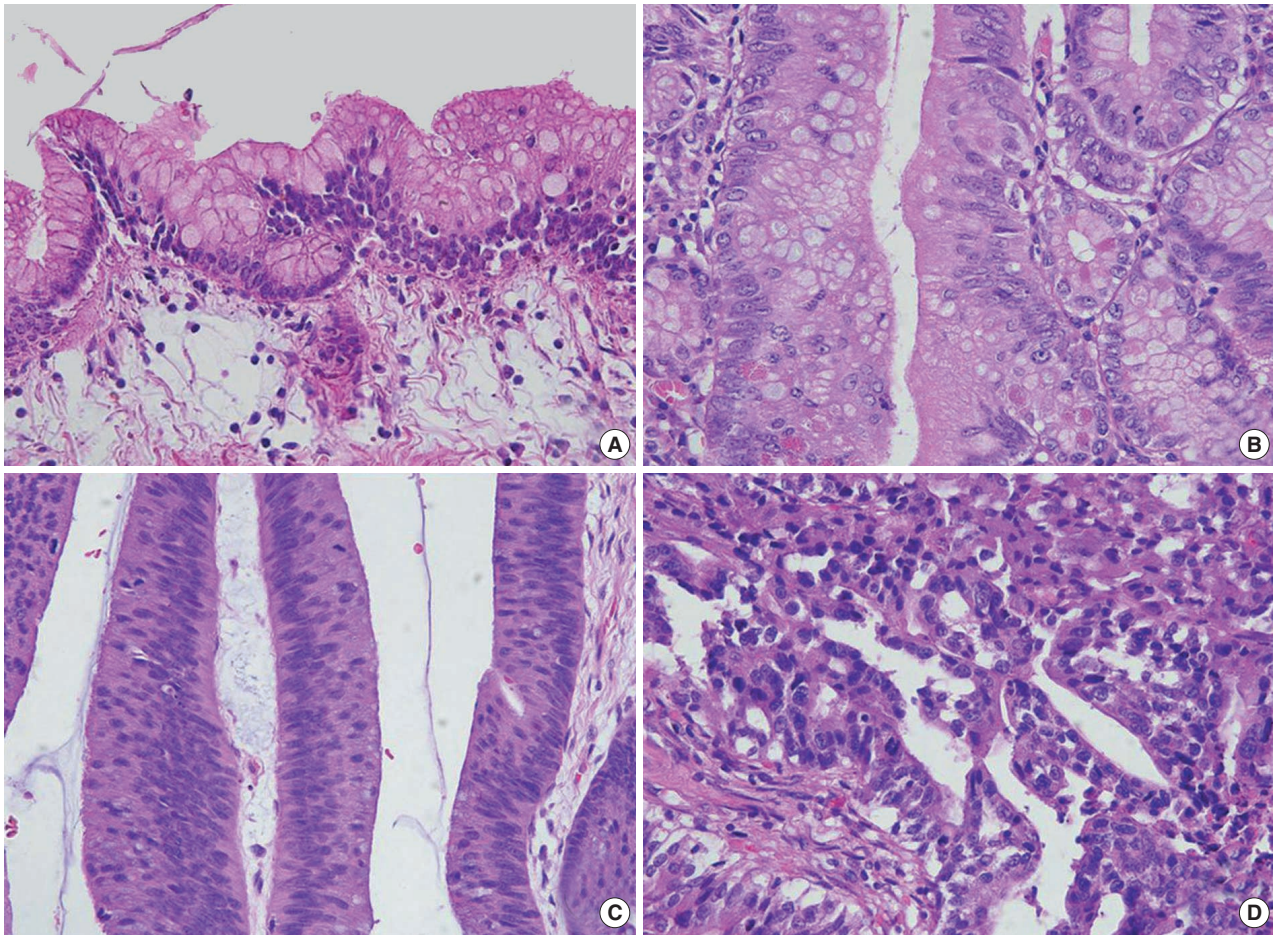

Fig. 2. Grade of dysplasia. (A) Benign intraductal papillary mucinous neoplasm (IPMN), (B, C) borderline IPMN, and (D) malignant IPMN.

applied only to the lesions involving small-caliber ducts less than 0.5 cm in diameter and divided into the following four categories.[6] PanIN-1A was defined as flat epithelial lesions composed of tall columnar cells with basally located small round to oval nuclei and abundant supranuclear mucin. PanIN-1B had a papillary, micropapillary or basally pseudostratified architecture, but was otherwise identical to PanIN-1A. PanIN-2 had some nuclear abnormalities including mild polarity loss, nuclear crowding, enlarged nuclei, pseudo-stratification and hyperchromasia. These nuclear abnormalities fall short of those seen in PanIN-3. PanIN-3 was characterized by a frank loss of nuclear polarity, dystrophic goblet cells, mitoses which may occasionally be abnormal, nuclear irregularities and prominent nucleoli.

Recurrence was defined as the presence of recurrent IPMN in the remnant pancreas after partial pancreatectomy, or as local, regional, or distant metastatic disease diagnosed during the follow-up period after resection of neoplasm. The recurrences were diagnosed by abdominal computed tomography and/or by histological examination of resected recurrent tumors and/or patient death due to recurrent or metastatic tumor.

The status of resection margin was classified in two ways. First, according to the size of the lesion, the resection margin status was classified as clear, involved by PanIN (lesions less than 0.5 cm), or involved by IPMN (lesions measuring 0.5 cm or more). Second, according to the grade of dysplasia, the resection margin status was classified as clear, involved by mild or moderate dysplasia, involved by severe dysplasia, or involved by invasive carcinoma. PanIN-1A, 1B and benign IPMN were equivalent to mild dysplasia, and PanIN-2 and borderline IPMN were equivalent to moderate dysplasia. When PanIN-3 or malignant non-invasive IPMN remained at the resection margin, the margin was designated to be involved by severe dysplasia.

Tissue microarray construction and immunohistochemistry

The classification of epithelial subtype was aided by mucin

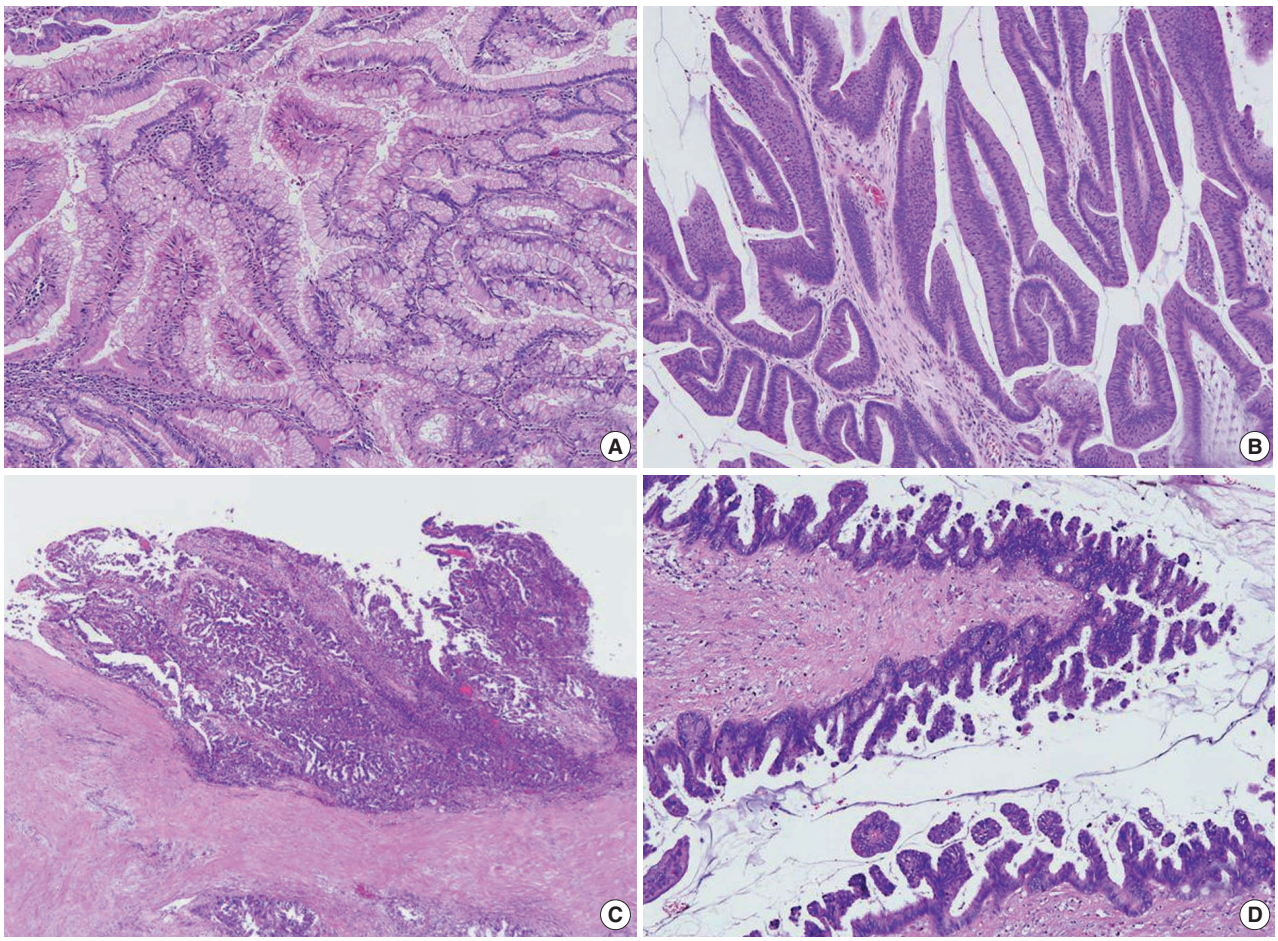

Fig. 3. Epithelial types of pancreatic intraductal papillary mucinous neoplasm. (A) Gastric type, (B) intestinal type, and (C, D) pancreatobiliary type.

phenotyping.[2,4] For equivocal cases, tissue microarrays were assembled with three cores of tissue from representative epithelium. The samples were obtained using a 1.5 mm-sized cylinder and were embedded in a recipient paraffin block. Immunohistochemical stains were performed on 4 μm-thick paraffin-embedded tissue sections, using heat-induced epitope retrieval, an avidin-biotin-peroxidase complex method, and an automated immunostainer (Ventana Benchmark, Tucson, AZ, USA). Antibodies to the following markers were used: mucin (MUC)-1 (1 : 200, Novo, Nottinghill, UK), MUC-2 (1 : 100, Novo), MUC-5AC (1 : 200, Novo) and MUC-6 (1 : 200, Novo). MUC-1-negative, MUC-2-negative and MUC-5AC-positive tumors were designated as gastric-type IPMN. The tumor was classified as intestinal-type IPMN when the epithelium expressed MUC-2 but not MUC-1, regardless of the expression of MUC-5AC. When the tumor expressed MUC-1 at least focally and did not express MUC-2, it was classified as pancreatobiliary type. The photographs of typical positive immunostainings for each MUC type are presented in Fig. 4.

Statistical analyses

Data were analyzed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Patient and disease-free survivals were determined by the Kaplan-Meier method. The patients were followed from the date of surgery to the date of death or recurrence. Patients, who died from other causes or were lost to follow-up, were censored from survival analysis. When comparing patient and disease-free survivals between two or more groups, the log-rank test was used. Association between clinical and pathologic variables was investigated using Pearson's χ^2 test for categorical variables and Student's t-test or one-way ANOVA for continuous variables. The results were considered statistically significant when the p-value was less than 0.05.

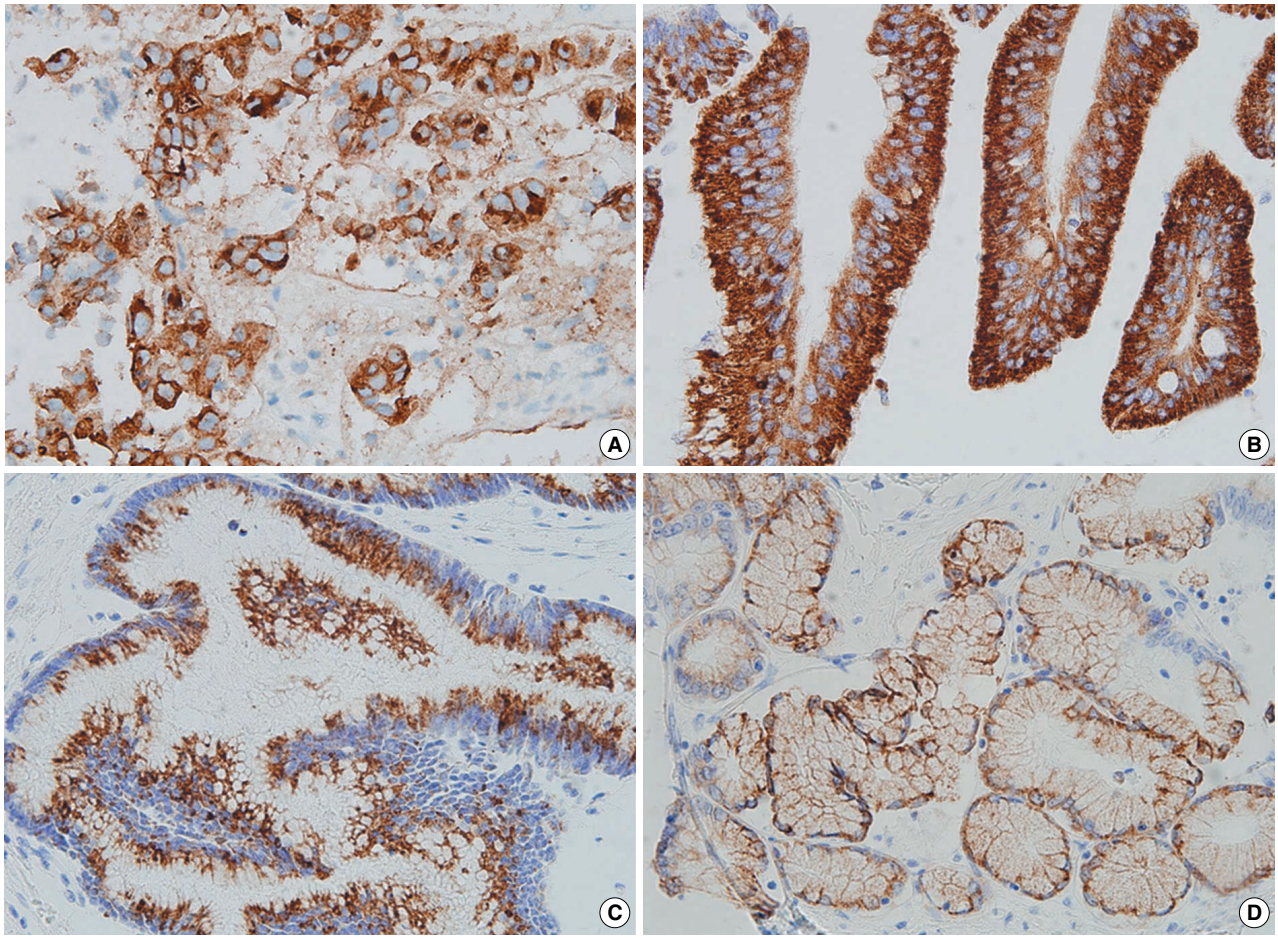

Fig. 4. Representative immunostainings for each mucin (MUC) type. (A) MUC-1, (B) MUC-2, (C) MUC-5AC, and (D) MUC-6.

RESULTS

Sixty cases (21.4%) were invasive carcinoma, and the 221 (78.6%) noninvasive cases included 87 cases (31.0%) of benign IPMN, 107 (38.1%) cases of borderline IPMN and 27 (9.6%) cases of malignant noninvasive IPMN. Main duct involvement was observed in 154 (54.8%) cases and the other 127 (45.2%) cases were of branch duct-type (Table 1). The histologic grade of main duct-type tumors was significantly higher than that of branch duct-type tumors ($p < 0.001$) and the main duct type tumors were significantly larger than the branch duct-type tumors (4.2 cm vs 2.9 cm, $p < 0.001$). In addition, tumor-related death and recurrence of the main duct-type tumors were more frequent than those of the branch duct-type tumors ($p = 0.009$ and $p = 0.011$).

When classified by the type of epithelium, gastric, intestinal and pancreatobiliary types were responsible for 218 (77.5%) cases, 39 (13.9%) cases and 24 (8.5%) cases, respectively (Table

Table 1. Clinicopathologic characteristics of main duct and branch duct type intraductal papillary mucinous neoplasm (IPMN)

Variables	Main duct type (%)	Branch duct type (%)	p-value
Frequency	154 (54.8)	127 (45.2)	
Diagnosis			< 0.001[a]
Noninvasive IPMN	109 (70.8)	112 (88.2)	
Benign	30 (19.5)	57 (44.9)	
Borderline	60 (39.0)	47 (37.0)	
Malignant noninvasive	19 (12.3)	8 (6.3)	
Invasive carcinoma	45 (29.2)	15 (11.8)	
Tumor size (cm)			< 0.001[b]
Mean	4.2	2.9	
Range	1-17	0.9-11	
Mortality	16 (10.4)	2 (1.6)	0.009[c]
Recurrence	27 (17.5)	6 (4.7)	0.011[c]

[a]A p-value is calculated by Pearson's χ^2 test comparing the relative frequencies of each diagnosis category between main duct and branch duct type IPMNs; [b]A p-value is calculated by Student t-test; [c]A p-value is calculated by log-rank test using Kaplan-Meier method.

2). Oncocytic type tumor was not found. The proportion of invasive carcinoma was highest in pancreatobiliary type IPMN (n = 13, 54.2%) followed by intestinal type (n = 11, 28.2%) and gastric type (n = 36, 16.5%), and their difference was statistically significant (p < 0.001). In addition, intestinal type IPMN was the largest (5.1 cm), followed by pancreatobiliary-type (4.5 cm) and gastric type IPMN (3.2 cm) (p < 0.001). The mortality and the recurrence rates were similar among all groups.

Before evaluating the relationship between resection margin status and recurrence, we divided all cases into two groups, the noninvasive IPMN group and the invasive carcinoma group, because invasiveness significantly increased the rate of tumor recurrence and shortened the time to recurrence (p = 0.001) (Fig. 5). As shown in Table 3, 20 cases recurred among 221 cases in the noninvasive IPMN group (9.0%) whereas 13 of 60 cases recurred in the invasive IPMN group (21.7%). In addition, within the noninvasive IPMN group, we further selected 71 patients with 5 years or longer follow-up period to analyze the disease-free survival rate in the noninvasive IPMN group because most of the noninvasive IPMN cases recurred quite late. Briefly, invasive carcinoma recurred earlier than noninvasive IPMN did after resection. The median time to recurrence was 4 years (range, 9 months to 6.8 years) in the noninvasive IPMN group and 8 months (range, 2 months to 4.8 years) in the invasive carcinoma group.

Among the 71 noninvasive IPMN cases with 5 years or more follow-up period, the cases where severe dysplasia remained at resection margins showed significantly lower disease-free survival than cases with clear resection margin (p = 0.030), although involvement of the resection margin by mild or moderate dysplasia did not significantly affect the recurrence rate (Fig. 6A). The recurrence rate was not different when the resection margin status was classified according to the size of the lesion at the resection margin (clear, involved by lesion < 0.5 cm or involved by lesion ≥ 0.5 cm) (Fig. 6B). In contrast to noninvasive IPMN cases, the invasive carcinoma cases showed a poor disease-free survival regardless of the grade of dysplasia (p =

Table 2. Clinicopathologic characteristics of each epithelial types of intraductal papillary mucinous neoplasm (IPMN)

Variables	Gastric (%)	Intestinal (%)	Pancreato-biliary (%)	p-value
Frequency	218 (77.6)	39 (13.9)	24 (8.5)	
Diagnosis				< 0.001[a]
Noninvasive IPMN	182 (83.5)	28 (71.8)	11 (45.8)	
Benign	82 (37.6)	4 (10.3)	1 (4.2)	
Borderline	82 (37.6)	19 (48.7)	6 (25.0)	
Malignant noninvasive	18 (8.3)	5 (12.8)	4 (16.7)	
Invasive carcinoma	36 (16.5)	11 (28.2)	13 (54.2)	
Tumor size (cm)				< 0.001[b]
Mean	3.2	5.1	4.5	
Range	0.9-17.0	1.0-17.0	1.5-13.0	
Mortality	14 (6.4)	1 (2.6)	3 (12.5)	0.264[c]
Recurrence	28 (12.8)	2 (5.1)	3 (12.5)	0.385[c]

[a]A p-value is calculated by Pearson's χ^2 test comparing the relative frequencies of each diagnosis category among three epithelial types; [b]A p-value is calculated by one-way ANOVA; [c]A p-value is calculated by log-rank test using Kaplan-Meier method.

Table 3. Recurrence rate according to resection marginal status in noninvasive intraductal papillary mucinous neoplasm (IPMN) and invasive carcinoma

Diagnosis	Residual lesion in resection margin	n	Recurrence (%)
Noninvasive IPMN	Overall	221	20 (9.0)
	Clear	131	8 (6.1)
	PanIN-1A	23	3 (13.0)
	PanIN-1B	23	2 (8.7)
	PanIN-2	5	1 (20.0)
	Benign IPMN	20	3 (15.0)
	Borderline IPMN	15	1 (6.7)
	Malignant noninvasive IPMN	4	2 (50.0)
Invasive carcinoma	Overall	60	13 (21.7)
	Clear	38	9 (23.7)
	PanIN-1B	5	0 (0.0)
	PanIN-3	1	0 (0.0)
	Benign IPMN	5	1 (20.0)
	Borderline IPMN	3	0 (0.0)
	Malignant noninvasive IPMN	4	1 (25.0)
	Invasive carcinoma	4	2 (50.0)

PanIN, pancreatic intraepithelial neoplasia.

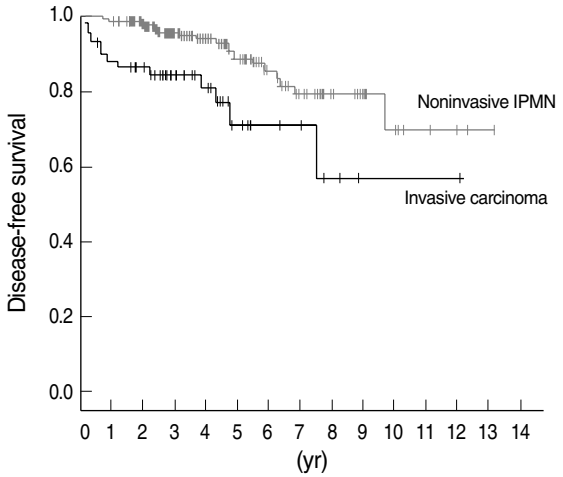

Fig. 5. Comparison of Kaplan-Meier curves of disease-free survival between noninvasive intraductal papillary mucinous neoplasm (IPMN) and invasive carcinoma groups. Disease-free survival is significantly lower in invasive carcinoma group than in noninvasive IPMN group (p = 0.001).

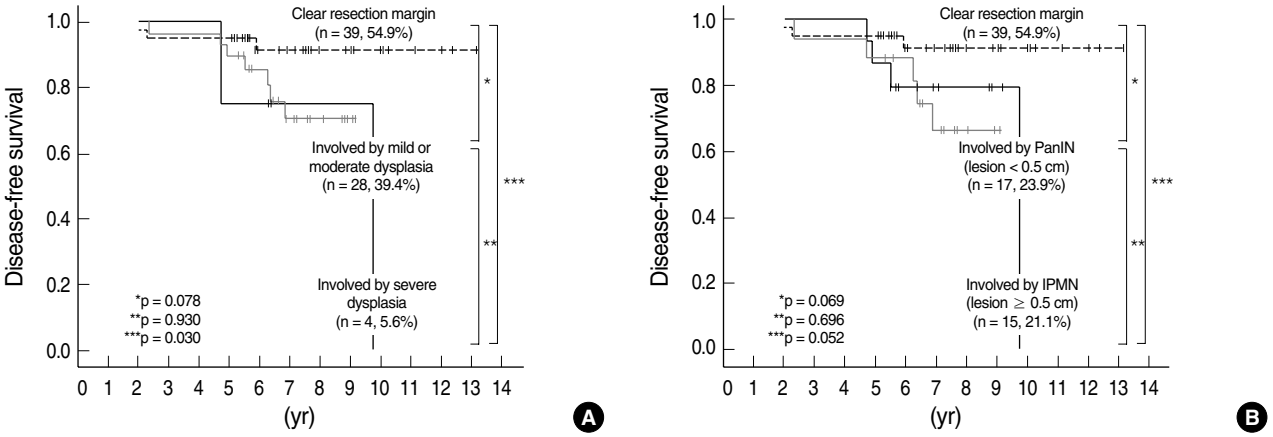

Fig. 6. Disease-free survivals according to resection marginal status in noninvasive intraductal papillary mucinous neoplasm (IPMN) group with five or more years of follow-up. (A) When categorized based on the grade of dysplasia involving the resection margin, severe dysplasia is associated with significantly lower disease-free survival than negative resection margin (***). (B) When categorized based on the tumor size, disease-free survivals are not different among each group.
PanIN, pancreatic intraepithelial neoplasia.

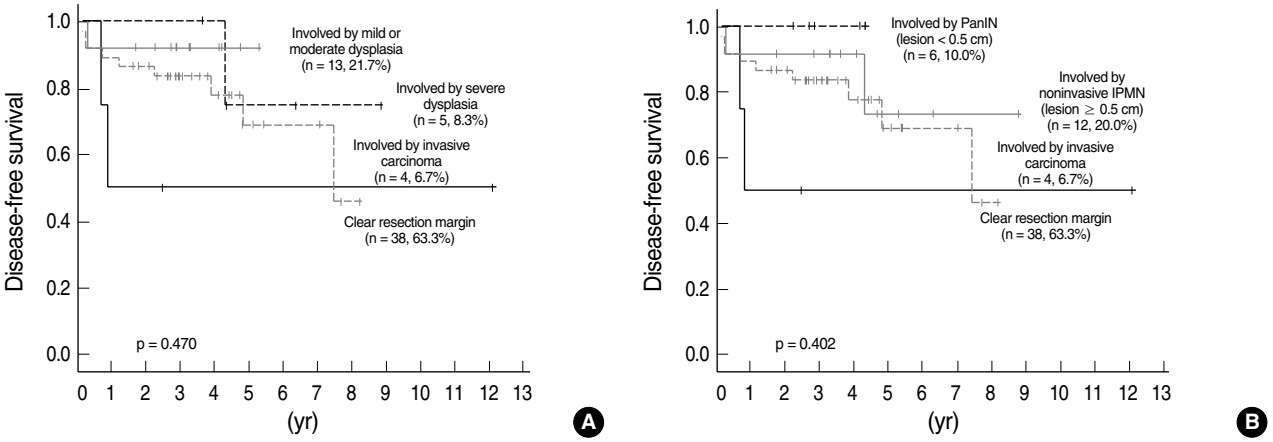

Fig. 7. Disease-free survivals according to resection marginal status in invasive carcinoma group. Resection marginal status is categorized according to the grade of dysplasia (A), or to the size (B) of residual lesions. The disease-free survival rates are not different among those categories.
IPMN, intraductal papillary mucinous neoplasm; PanIN, pancreatic intraepithelial neoplasia.

0.470) or the size (p = 0.402) of residual lesion at the resection margin (Fig. 7).

Detailed analysis of recurrent cases revealed some intriguing or interesting cases (Table 4). Five of 87 benign IPMNs (5.7%) developed recurrent tumors. Among those five cases, two cases were free from tumor cells, one case was involved by PanIN-1A and two cases were involved by benign IPMN at their resection margins. In particular, one benign IPMN case, the resection margin of which was clear, developed a histologically proven poorly differentiated carcinoma in the remaining pancreas after four years. Among 107 borderline IPMN cases, ten patients (9.3%) developed recurrent tumors and five patients of those died of peritoneal seeding or liver metastasis. The resection margin status of these five cases of borderline IPMNs which showed fatal outcomes, was free from tumor in two cases, and involved by PanIN-1A or borderline IPMN in the others. Five of 27 malignant noninvasive IPMN cases (18.5%) developed recurrent tumors. Three of the 27 cases had no tumor cells at the resection margin while the rest of the cases harbored malignant noninvasive IPMN at the resection margin. One case of malignant noninvasive IPMN, the resection margin of which was free from tumor, presented with metastases in the lung and the patient died 3.4 years after surgery. It is also noteworthy that among 38 invasive carcinomas which had been free from tumor at their resection margins, nine cases (23.7%) developed recurrent tumor (Table 3) and that most of them (8 of 9 patients) eventually died

Table 4. Resection margin (RM) status and clinical outcomes of 20 recurrent noninvasive intraductal papillary mucinous neoplasms (IPMNs)

Sex/Age	Diagnosis category	Residual lesion in RM	Time to recurrence (yr)	Outcome	Time to death (yr)
M/60	Benign	Clear	2	Alive[a]	
M/58	Benign	Clear	4.4	Alive/carcinoma in remnant pancreas with lymph node metastasis[b]	
M/60	Benign	Benign IPMN	2.5	Alive[a]	
M/61	Benign	Benign IPMN	5.5	Alive[a]	
F/60	Benign	PanIN-1A	6.3	Alive[a]	
M/37	Borderline	Clear	2.3	Alive[a]	
M/66	Borderline	Clear	2.1	Dead[a] (liver metastasis)	3.5
F/67	Borderline	Clear	3.1	Dead (peritoneal seeding)	3.8
M/55	Borderline	Benign IPMN	4.9	Dead (peritoneal seeding)	5.2
M/69	Borderline	Borderline IPMN	0.8	Dead (peritoneal seeding)	1
F/60	Borderline	PanIN-1A	2.3	Alive[a]	
M/57	Borderline	PanIN-1A	0.9	Dead (peritoneal seeding)	1.3
M/46	Borderline	PanIN-1B	4.7	Alive[a]	
M/56	Borderline	PanIN-1B	6.3	Alive[a]	
M/62	Borderline	PanIN-2	6.8	Alive[a]	
M/65	Malignant noninvasive	Clear	5.9	Alive[a]	
F/63	Malignant noninvasive	Clear	2.5	Alive[a]	
M/72	Malignant noninvasive	Clear	3.7	Dead (lung metastasis)	3.7
M/61	Malignant noninvasive	Malignant noninvasive	4.7	Alive[a]	
F/58	Malignant noninvasive	Malignant noninvasive	9.7	Alive[a]	

[a] Alive with recurrent cystic tumor on abdominal computed tomography scan; [b] Histologically proven after second operation.
M, male; F, female; PanIN, pancreatic intraepithelial neoplasia.

of disease.

DISCUSSION

By detailed analysis of a large series of consecutive IPMN cases, we found that the recurrence rate of noninvasive IPMNs was significantly increased when severe dysplasia was present at the resection margin. The recurrence rate of noninvasive IPMNs with resection margins positive for lesions other than severe dysplasia was found to be similar to that of cases with negative resection margins. These results are in line with other studies regarding margin involvement of noninvasive IPMN.[3,13,16,17] In addition, mucinous hyperplasia (PanIN-1A or 1B) is observed not only in ducts around pancreatic ductal adenocarcinoma or IPMN but also in chronic pancreatitis or other non-neoplastic diseases.[13] Therefore it could be proposed that further resection might not be necessary unless the resection margin is involved by severe dysplasia upon intraoperative consultation.

The patient and disease-free survival rate were lower in main duct-type than in branch duct-type, in line with other studies.[3,9,14,15,18] This seems to be because IPMNs involving main ducts are larger and more frequently invasive than those confined to branch ducts. Similarly, intestinal and pancreatobiliary type IPMNs tended to be of higher grade than gastric type IPMNs. These results are generally compatible with the previous studies where intestinal type and pancreatobiliary type IPMN are more likely to be malignant or invasive carcinoma than gastric type and therefore show worse prognosis.[3,5,19] However, in our study the recurrence rate of intestinal or pancreatobiliary type was not significantly different from that of gastric type. This may be because the numbers of intestinal and pancreatobiliary type IPMN were too small to reach statistical significance. In addition, intestinal type IPMNs have generally been reported to be slightly more frequent than gastric type IPMNs.[2,3,16,19] However, gastric type IPMNs were observed much more frequently than intestinal type IPMNs in this study. The reason for this observation is uncertain, but it might reflect the geographical or ethnic difference in disease pattern.

Recurrence rates may be underestimated in noninvasive IPMNs when the follow-up period is short, because IPMNs are usually slow-growing tumors, with recurrence becoming evident late in the disease course.[13] Some studies with short term follow-up (up to 3 years) reported near zero recurrence in noninvasive IPMNs.[11,20] In contrast, recurrences were occasionally reported in patients with a long follow-up period (more than 3

years).[13,15] In our series, the recurrence rate of noninvasive IPMNs was 9.0% when all cases were analyzed, but it was increased to 16.9% when the analysis was restricted to cases with five or more years of follow-up. In addition, 30% of recurrent tumors occurred five years after the resection. These results suggest that long term follow-up is required to estimate recurrence rate accurately.

Although rare, recurrences after resection of noninvasive IPMNs have been reported by several studies and some of the recurrences occurred in cases with negative margins.[3,7,13,14] Likewise, some resected noninvasive IPMNs with clear margins recurred in our series, raising the possibility of multifocal disease with synchronous tumor in the remnant pancreas, or later development of *de novo* tumors in the remnant pancreas because of a neoplastic tendency of the entire ducts.

One benign IPMN, five borderline IPMNs and one malignant noninvasive IPMN in our series recurred as metastatic tumors and all but one recurrence from benign IPMN resulted in patient death. Similar findings have also been reported by others.[13,21] Regarding to the reason, we suggest that invasive components might have been undetected in resected specimens because of inadequate sampling. This explanation is further evidenced by the fact that all seven cases recurred within five years after resection, and that three cases (two borderline IPMNs and one malignant noninvasive IPMN) recurred as metastatic carcinoma even when the resection margins were negative. Similarly, 92.3% of the invasive carcinomas recurred within five years from the time of resection and 63.3% of the cases were free from tumor at the resection margin. Therefore, it should be recommended that extensive sampling be done during the pathological examination of resected IPMNs.

In the cases of invasive IPMN, the recurrence rate was significantly higher than in noninvasive IPMNs ($p = 0.001$) and was not dependent on the status of the resection margin. This means that invasiveness *per se* is a strong risk factor for recurrence. Chari *et al*.[13] showed that invasive IPMNs frequently recurred even after complete resection and concluded that total pancreatectomy was unlikely to prevent recurrence in patients with invasive IPMN. They hypothesized that extrapancreatic tumor spread through micrometastases in the early phase of invasion. Similar conclusions were drawn by others reporting that recurrences in the form of disseminated disease (3.4-44%) outnumbered pure local recurrences in remnant pancreases (0-15%).[9] In the present study, eight (61.5%) of 13 recurrences presented themselves as metastatic disease. Based on our results and those of others,[9,13] the benefit of extended or total pancreatectomy to obtain negative resection margin in invasive carcinoma is questionable. However, we should first consider the possibility of overlooked residual invasive carcinoma at the retroperitoneal resection margin due to inadequate sampling. Therefore, further investigation of the benefit of clearing the resection margin in invasive carcinoma arising in pancreatic IPMN is needed after more thorough examination with extensive sampling of retroperitoneal resection margins.

In conclusion, the presence of severe dysplasia at the resection margin best predicts recurrence in noninvasive IPMN cases and stromal invasion *per se* is the strongest risk factor for recurrent or metastatic disease regardless of the resection margin status. Notably, involvement of resection margin by mild or moderate dysplasia did not affect the recurrence rate. These results have an important clinical implication because aggressive total resection of the pancreas results in serious metabolic complications. Therefore, it can be stated that the recognition of severe dysplasia is important during intraoperative consultations for resection margin and that a conservative approach might be acceptable unless severe dysplasia is found at the resection margin. In addition, extensive sampling is required in the pathologic evaluation of resected IPMN cases.

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