Long-term Prospective Cohort Study of Patients Undergoing Pancreatectomy for Intraductal Papillary Mucinous Neoplasm of the Pancreas

Implications for Postoperative Surveillance

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Objective: To evaluate long-term follow-up results after surgical treatment of intraductal papillary mucinous neoplasm (IPMN) to optimize postoperative surveillance strategies.

Background: Little is known about the postoperative natural history of IPMN, especially about long-term follow-up results in patients with benign or noninvasive IPMN.

Methods: Long-term follow-up was undertaken in a prospective cohort of 403 consecutive patients who underwent surgical treatment of IPMN at Seoul National University Hospital. Of these, 37 patients with ductal adenocarcinoma arising in IPMN were excluded from the analysis.

Results: Of the 366 patients, 82 had low-grade dysplasia, 171 had intermediate-grade dysplasia, 45 had high-grade dysplasia, and 68 had IPMN with associated invasive carcinoma. During a median follow-up of 44.4 months, the overall recurrence rate was 10.7%. Pathologic grade of dysplasia was associated with recurrence rate ($P < 0.001$). IPMNs involving main duct had higher rate of recurrence ($P = 0.021$). Of the 298 patients with benign or noninvasive IPMN, 16 (5.4%) had recurrences including distant metastasis. Multivariate analysis revealed that the degree of dysplasia was the most important predictor of recurrence ($P < 0.001$). The overall 5-year disease-free survival rate was 78.9% and was significantly lower in patients with high-grade dysplasia than in those with low- or intermediate-grade dysplasia ($P = 0.045$).

Conclusions: Pancreatic IPMNs recur in 10.7% of patients. Recurrence is correlated with the degree of dysplasia, and 5.4% of patients with benign or noninvasive IPMN have recurrences including distant metastasis. Thorough postoperative surveillance is needed not only for patients with invasive IPMN but also for those with benign or noninvasive IPMN, especially for patients with high-grade dysplasia.

Keywords: intraductal papillary mucinous neoplasm, pancreas, prognosis, recurrence, surveillance

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are precursors of pancreatic ductal adenocarcinoma (PDAC). Imaging modalities and endoscopic cytology have been used for the preoperative surveillance and prediction in patients with such malignancy. Less is known, however, about the postoperative surveillance of these patients, including modes of surveillance, length of time, and the need for adjuvant treatments. Although IPMN has a favorable prognosis,[1,2] its recurrence patterns have not been assessed in detail. Several studies have described the fate of the remnant pancreas,[3] residual IPMN,[4] and risk factors for recurrence,[5–7] but few large-scale studies have included regular, long-term follow-up of a cohort of IPMN patients who underwent surgical treatment. Knowledge of recurrence patterns after surgical treatment of IPMN is important for establishing a postoperative surveillance strategy and to decide whether to administer adjuvant treatment. Because disseminated metastases have been reported, even in patients with noninvasive IPMNs,[8–10] detailed recurrence patterns should be analyzed according to the degree of dysplasia. Moreover, although main duct–type IPMN is considered to be more malignant than branch duct–type IPMN, recurrence according to IPMN type has not been well documented and there is no difference in postoperative surveillance or treatment strategy based on the initial IPMN type. Using a large, prospective cohort of IPMN patients who underwent surgical treatment, we analyzed recurrence patterns according to the degree of dysplasia and IPMN type to establish postoperative surveillance strategies in IPMN patients who have undergone pancreatectomy.

MATERIALS AND METHODS

This study was approved by our institutional review board. Since 1995, a total of 403 consecutive patients have undergone surgical treatment of IPMN at Seoul National University Hospital. Surgical indications followed international consensus guidelines,[11] including for main duct–type IPMNs, branch duct–type IPMNs with cysts larger than 30 mm, main pancreatic duct dilatation exceeding 5 mm, the appearance of new mural nodules, or the presence of any symptoms. Surgery was also performed when cysts showed significant growth or when there was increased suspicion of malignancy.[12] Postoperative adjuvant treatment was not performed in patients with low-, intermediate-, or high-grade dysplasia, and those with invasive IPMN followed the protocol of PDAC based on 5-fluorouracil or gemcitabine chemotherapy and radiation therapy.

Interpretation of Pathologic Diagnosis and IPMN Type

Pancreas specimens were serially sectioned at 5- to 7-mm intervals, and whole slides were reviewed by a specialized pathologist (K.B.L.) with 12 years of experience. The degree of dysplasia was classified according to the fourth edition of the WHO classification[13] as low-, intermediate-, or high-grade dysplasia or IPMN with associated invasive carcinoma. IPMN with associated invasive carcinoma included only the invasive IPMN, and 37 PDACs—ductal adenocarcinoma arising in IPMN—diagnosed according to the proportion of

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invasive component and morphologic characteristics were excluded from analysis.[14]

Main duct–type IPMN was radiologically defined as an IPMN involving the main pancreatic duct without cystic dilatation greater than 1 cm of the surrounding branch ducts.[15] Branch duct–type IPMN was defined as cystic dilatation of the branch pancreatic ducts or the presence of a pancreatic mucinous cyst communicating with the pancreatic duct without main duct dilatation.[11] Mixed-type IPMN was defined as having radiologic characteristics of both main and branch duct–type IPMNs, with main duct dilatation above 5 mm.[1]

Postoperative Surveillance and Detection of Recurrence

Patients were evaluated postoperatively every 3 months for the first year and every 6 months for the second year. Subsequently, patients with noninvasive tumors were examined yearly, whereas patients with invasive tumors followed the protocol for PDAC (tumor marker test every 3 months and abdominal computed tomography every 6 months). Surveillance included clinical evaluations, routine laboratory tests, and imaging examinations, including computed tomography or magnetic resonance imaging. Tumor recurrence detected with computed tomography or magnetic resonance imaging was confirmed by biopsy if possible. Recurrences resulting from malignancies in other organs were not included in the analysis. Remnant pancreatic cysts were thoroughly examined, and the occurrence of new IPMNs was monitored. Although most newly occurring IPMNs in the remnant pancreas remain stable and do not increase the risk for development of invasive disease or reduce survival,[3,4] all recurrent IPMNs were included in the analysis of recurrence patterns.

Statistical Analysis

All statistical analyses were performed using IBM SPSS, version 19.0 (IBM Corp, Somers, NY). Nominal variables were compared using the χ^2 test or the Fisher exact test, and continuous variables were compared using the Student *t* test or analysis of variance. For binary variables, a logistic regression model was used to find significant predictors and estimate their odds ratios. Two-sided *P* values less than 0.05 were considered statistically significant. Survival was analyzed using the Kaplan-Meier method and compared by the log rank test.

RESULTS

Patient Demographics

Demographic findings of the study subjects are listed in Table 1. Main duct dilatation above 5 mm was present in 39.3% of the patients, and 54.1% of the lesions were located in the pancreatic head. Of the 366 patients, 30 (8.2%) underwent total pancreatectomy. Invasive IPMNs were observed in 68 patients (18.6%).

Overall Recurrence

After a median follow-up of 44.4 months (range, 0.4–214.4 months), 39 of the 366 patients (10.7%) experienced disease recurrence (Fig. 1) at a median of 18.3 months (range, 2.5–84.3 months). Of these 39 patients, 16 (41.0%) did not initially have invasive IPMN.

Analysis of types of disease recurrence showed that 12 patients (3.3%) had recurrent IPMN in the remnant pancreas, 4 (1.1%) had pancreatic cancers, 9 (2.5%) had locoregional recurrences, and 24 (6.6%) had systemic recurrences, including 10 cases of liver metastases, 10 cases of peritoneal seeding, and 11 cases of lung metastases. Twelve patients had multiple recurrence sites, including locoregional recurrences and liver/peritoneal/lung metastasis. Six of the 39 patients (15.4%) underwent surgical treatment, 28 received medical treatment, and the remaining 5 patients underwent continuous postoperative surveillance because of newly developed IPMNs that did not meet surgical indications. At the end of the follow-up period, 9 patients had died from recurrent disease.

TABLE 1. Patient Demographics (N = 366)

Age, mean (SD), yr	63.7 (9.0)
Sex, M:F	1.59:1
CEA, median (range)	1.7 (0–475)
CA19-9, median (range)	10.0 (0–12,100)
IPMN type	
Main duct	26 (7.1%)
Branch duct	222 (60.7%)
Mixed	118 (32.2%)
Location	
Head	198 (54.1%)
Body, tail	131 (35.8%)
Diffuse	37 (10.1%)
Cyst size, mean (SD), cm	3.1 (1.4)
Main pancreatic duct size, mean (SD), mm	5.7 (6.8)
Operation	
Whipple	35 (9.6%)
PPPD	131 (35.8%)
Distal, subtotal	134 (36.6%)
Total	30 (8.2%)
Median	9 (2.5%)
DPRHP, PHRSD	15 (4.1%)
Enucleation	12 (3.3%)
Pathology	
Low-grade dysplasia	82 (22.4%)
Intermediate-grade dysplasia	171 (46.7%)
High-grade dysplasia	45 (12.3%)
Invasive IPMN	68 (18.6%)

CA19-9 indicates cancer antigen 19-9; CEA, carcinoembryonic antigen; DPRHP, duodenum-preserving resection of the head of the pancreas; PHRSD, pancreas head resection with segmental duodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy.

Fate of Remnant IPMN and Occurrence of New IPMNs During Follow-up

Of the 366 patients, 22 (6.0%) had remnant IPMN in the remnant pancreas after operation. Remnant IPMN was diagnosed according to radiologic diagnostic criteria for IPMN as described earlier. Twenty of these patients had branch duct–type IPMNs that did not meet the indications for surgery, and 2 patients had main pancreatic dilatation in the remnant pancreas. Two patients had cyst growth during follow-up that did not reach indications for surgery. Two patients had main duct dilatation that remained stable. To date, none of these 22 patients has required surgical treatment of remnant IPMN in the remnant pancreas.

Five patients (1.4%) developed new IPMNs during follow-up, including 4 who developed branch duct–type IPMNs that did not meet the indications for surgery and 1 who developed main pancreatic duct dilatation. No patient underwent surgical treatment because of newly developed IPMNs.

Recurrence Patterns According to Initial Pathology

Table 2 summarizes the relationship between recurrence pattern and initial IPMN pathology, excluding recurrences resulting from other organ malignancy. Recurrence rate significantly increased as the grade of dysplasia increased. The rate of recurrence was significantly higher in patients with invasive IPMN than in patients with high-grade dysplasia (33.8% vs 13.3%; $P = 0.014$) and was significantly higher in patients with high-grade dysplasia than in patients with low- and intermediate grade IPMNs (13.3% vs 4.0%; $P = 0.027$). Rates

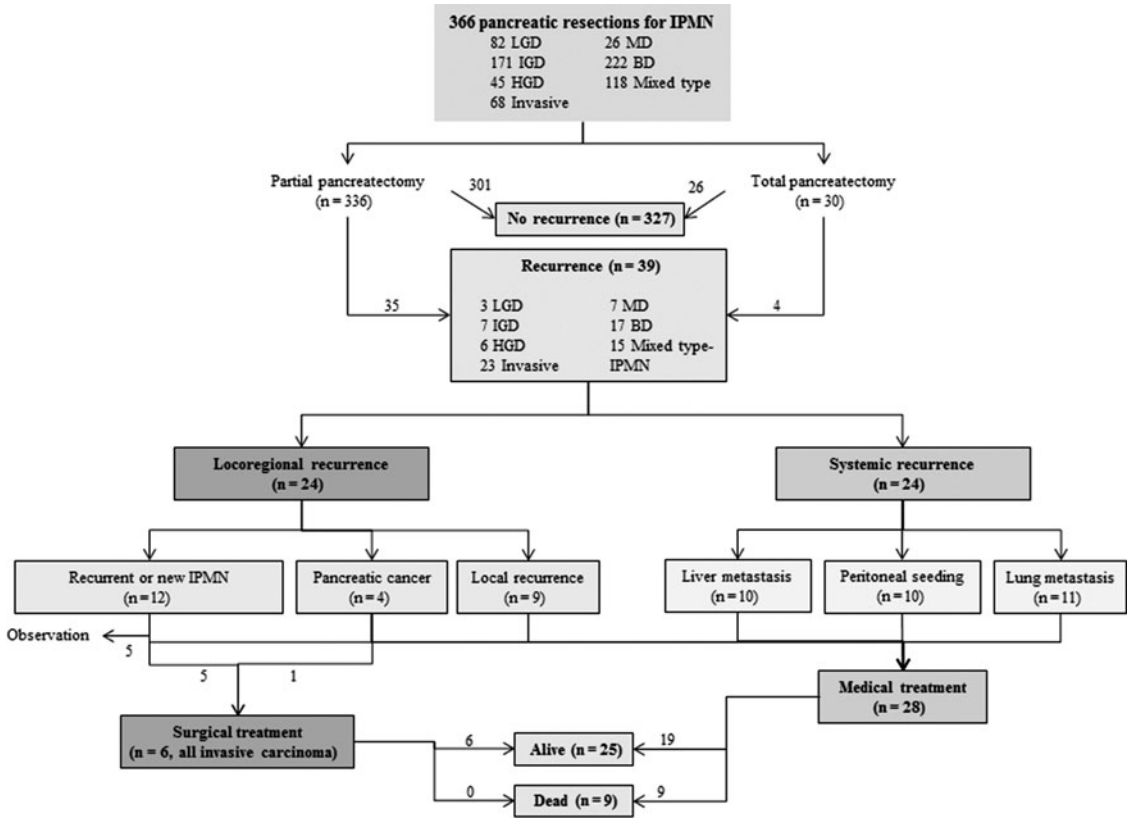

FIGURE 1. Patient flow. BD indicates branch duct; HGD, high-grade dysplasia; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia; MD, main duct.

TABLE 2. Recurrence Pattern According to Pathology

	LGD, IGD (n = 253)	HGD (n = 45)	Invasive IPMN (n = 68)	*P*	Total (N = 366)
Recurrence	10 (4.0%)	6 (13.3%)	23 (33.8%)	<0.001	39 (10.7%)
IPMN	6 (2.4%)	2 (4.4%)	4 (5.9%)	0.562	12 (3.3%)
Pancreas cancer	1 (0.4%)	1 (2.2%)	2 (2.9%)	0.505	4 (1.1%)
Locoregional	1 (0.4%)	0	8 (11.8%)	<0.001	9 (2.5%)
Liver	2 (0.8%)	1 (2.2%)	7 (10.3%)	<0.001	10 (2.7%)
Seeding	1 (0.4%)	1 (2.2%)	8 (11.8%)	<0.001	10 (2.7%)
Lung	0	1 (2.2%)	10 (14.7%)	<0.001	11 (3.0%)
DFS, median (range), mo	52.1 (0.4–213.5)	29.4 (2.0–166.8)	18.1 (2.5–214.4)		41.5 (0.4–214.4)

HGD indicates high-grade dysplasia; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia.

of recurrence as IPMN in the remnant pancreas or PDAC were comparable in patients with various degrees of dysplasia, whereas local recurrences and liver, peritoneal, and lung metastases occurred more often in patients with invasive IPMN than in those with noninvasive IPMN.

Recurrence Patterns According to IPMN Type

The relationship between recurrence pattern and IPMN type is shown in Table 3. The recurrence rate was higher in patients with IPMNs involving main pancreatic duct than branch duct–type IPMNs ($P = 0.021$). The rate of recurrence as IPMNs in the remnant pancreas requiring surgical treatment was significantly higher in patients with main duct–type IPMNs than in those with mixed or branch duct–type IPMNs (15.4% vs 0.5% and 1.7%; $P < 0.001$). The rates of development of PDAC, local recurrence, liver, and lung metastases were comparable among patients with the 2 IPMN types, whereas peritoneal seeding was more frequent in patients with IPMNs involving main pancreatic duct.

Recurrence Patterns According to Histologic Subtype

Slides for a review of histologic subtypes of IPMN were available for 295 of the 366 patients (80.6%). Of these 295 patients, 190 had gastric, 56 had intestinal, 43 had pancreatobiliary, and 6 had oncocytic IPMNs. Their recurrence rates were 4.7%, 12.5%, 30.2%, and 0%, respectively ($P < 0.001$). The proportion of invasive IPMNs in these 4 groups was 5.8%, 26.8%, 58.1%, and 83.3%, respectively ($P < 0.001$). Rates of local recurrence were significantly higher for

TABLE 3. Recurrence Pattern According to IPMN Type

	Main and Mixed (n = 144)	Branch (n = 222)	*P*	Total (N = 366)
Recurrence	22 (15.3%)	17 (7.7%)	0.021	39 (10.7%)
LGD, IGD	3/65	7/188		10/253 (4.0%)
HGD	3/31	3/14		6/45 (13.3%)
Invasive IPMN	16/48	7/20		23/68 (33.8%)
Recurrence site				
IPMN	6 (4.2%)	6 (2.7%)	0.640	12 (3.3%)
Pancreatic cancer	1 (0.7%)	3 (1.4%)	0.938	4 (1.1%)
Locoregional	4 (2.8%)	5 (2.3%)	0.975	9 (2.5%)
Liver	5 (3.5%)	5 (2.3%)	0.710	10 (2.7%)
Seeding	8 (5.6%)	2 (1.0%)	0.019	10 (2.7%)
Lung	6 (4.2%)	5 (2.3%)	0.462	11 (3.0%)
DFS, median (range), mo	32.8 (2.0–187.8)	52.4 (0.4–214.4)		41.5 (0.4–214.4)

HGD indicates high-grade dysplasia; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia.

patients with pancreatobiliary type IPMNs than for patients with gastric and intestinal type IPMNs (7.0% vs 0% vs 0.5%; $P = 0.034$), as were rates of lung metastasis (9.3% vs 0% vs 0.5%; $P = 0.003$).

Among benign and noninvasive IPMNs, recurrence rates were 3.4%, 9.8%, 11.1%, and 0% for gastric, intestinal, pancreatobiliary, and oncocytic types, respectively ($P = 0.062$). Pancreatobiliary type developed more frequent recurrent branch- or main duct–type IPMNs in the remnant pancreas than in the intestinal and gastric types (11.1% vs 7.3% vs 0.6%, respectively; $P = 0.036$). Rates of local recurrence, liver, lung, or peritoneal metastasis were comparable between subtypes.

Recurrence Patterns According to Operation Methods and Resection Margin

Nine patients with main duct–type IPMN, 4 with branch duct–type IPMN, and 17 with mixed-type IPMN underwent total pancreatectomy. Two patients with low-grade dysplasia in the pancreatic tail underwent total pancreatectomy due to cancer of the combined ampulla of Vater. Of the remaining 28 patients, 9 had intermediate-grade dysplasia, 6 had high-grade dysplasia, and 13 had invasive IPMN. Recurrence rates were similar in patients who underwent total and partial pancreatectomies (16.7% vs 10.2%; $P = 0.421$), and all 5 patients who had recurrence after total pancreatectomy had systemic metastases.

Of all 366 patients, 15 (4.1%) had mucinous hyperplasia, 31 (8.5%) had low-grade dysplasia, 18 (4.9%) had intermediate-grade dysplasia, and 1 (0.3%) had high-grade dysplasia at the resection margin. Of these 65 patients, 7 (10.8%) experienced disease recurrence. Two patients with low- and intermediate-grade dysplasia had locoregional recurrence, and the remaining 5 experienced distant metastasis, with 1 having mucinous hyperplasia, 1 low-grade dysplasia, and 3 intermediate-grade dysplasia at the resection margin. The patient who had high-grade dysplasia at the resection margin did not experience recurrence after 85.7 months of follow-up. Positive resection margin was not a significant predictor of recurrence (12.1% vs 10.4%; $P = 0.704$).

Recurrences After Resection of Benign or Noninvasive IPMN

Of the 298 patients who underwent resection for noninvasive IPMNs, 16 (5.4%, Table 4) experienced recurrences after a median of 47.4 months (range, 0.4–213.5 months). Two of these patients, with initial main duct–type IPMN, developed recurrent IPMNs in the remnant pancreas requiring surgery. The remaining 14 patients experienced recurrence after resection of initially benign or noninvasive branch duct–type IPMN. Of these 14 patients, one initially had low-grade dysplasia, along with a synchronous early gastric cancer that was curatively resected. After 68.8 months, this patient had an unresectable pancreas mass with liver metastasis (Fig. 2). Of the remaining 13 patients with initially benign or noninvasive branch duct–type IPMN, 2 had low-grade dysplasia, 6 had intermediate-grade dysplasia, and 5 had high-grade dysplasia. Six had recurrences of IPMNs in the remnant pancreas, 1 had pancreatic cancer, and 6 had distant metastasis without local recurrence. At the end of follow-up, 4 of these 16 patients had died from disease whereas the other 12 remain alive after a median of 43.6 months.

Recurrences Requiring a Second Operation

Eight of the 39 patients who had recurrences (20.5%) required surgical treatment (Table 5). Of these 8 patients, 2 had intermediate-grade dysplasia, 2 had high-grade dysplasia, and 4 had invasive IPMN. Four of these patients had main duct–type IPMN and 4 had branch duct– or mixed-type IPMN. Five patients underwent curative resection of the recurrent disease, and 1 patient underwent a bypass operation due to a locally advanced disease. All of these patients remain alive after the second operation for 2.6 to 99.7 months.

Overall Survival and Disease-Free Survival After Surgical Treatment of IPMN

The 5-year overall survival rate of the 366 patients was 86.6%. The overall survival rate was inversely associated with the degree of dysplasia, being 72.2% in patients with invasive IPMN, 83.2% in patients with high-grade dysplasia, and 90.2% in patients with low- to intermediate-grade dysplasia ($P = 0.003$). The overall 5-year disease-free survival (DFS) rate was 78.9%, with DFS also inversely associated with the grade of dysplasia of the initial tumor (Fig. 3A, $P < 0.001$). Patients with high-grade dysplasia had significantly poorer prognosis than among those with low- and intermediate-grade dysplasia ($P = 0.045$) but significantly better prognosis than patients with invasive IPMN ($P = 0.005$). IPMNs involving main pancreatic duct had significantly lower DFS than those with branch duct–type IPMNs (Fig. 3B, $P = 0.030$).

Univariate analysis showed that the risk of recurrence was higher in patients with cancer antigen 19-9 levels more than 37 U/mL (vs ≤37 U/mL), in those with high-grade dysplasia or invasive IPMN (vs low- to intermediate-grade dysplasia), and in those with IPMNs involving main pancreatic duct (vs branch duct–type IPMNs). Multivariate analysis showed that the degree of dysplasia was the single

TABLE 4. Recurrence After Resection of Benign or Noninvasive IPMN

Age/Sex	Initial IPMN Type	Initial Operation	Initial Pathology	Initial Resection Margin	DFS	Recurrence Site	Treatment	Combined Disease	Final Status
73/F	Branch	Enucleation	LGD	(−)	68.8 mo	Unresectable pancreas mass, liver mets	Chemotherapy	EGC	Alive, 95.7 mo
63/F	Branch	Distal	LGD	(−)	35.7 mo	Remnant pancreas IPMN	Observation		Alive, 103.3 mo
72/M	Branch	PPPD	LGD	(−)	45.0 mo	Remnant pancreas IPMN	Observation		Alive, 91.0 mo
55/M	Branch	Distal	IGD	(−)	55.6 mo	Remnant pancreas IPMN	Remnant total → IPMC T3N0		Alive, 155.3 mo
46/M	Branch	Median	IGD	(+), LGD	32.4 mo	Local soft tissue	Chemotherapy		Alive, 47.2 mo
67/F	Branch	Distal	IGD	(−)	80.3 mo	Remnant pancreas IPMN	Observation		Alive, 94.8 mo
77/M	Branch	Distal	IGD	(−)	21.2 mo	Remnant pancreas IPMN	Observation		Alive, 21.8 mo
57/M	Mixed	PPPD	IGD	(−)	35.9 mo	Liver mets	Supportive care	EGC	Alive 44.6 mo
57/F	Mixed	Whipple	IGD	(+), IGD	34.6 mo	Ovary, peritoneal seeding	TAH, BSO, Chemotherapy		Dead, 38.8 mo
41/M	Main	Distal	IGD	unknown	40 mo	Remnant pancreas IPMN	Remnant total → IPMC T2N0		Alive, 72.6 mo
77/F	Branch	PPPD	HGD	(−)	3.7 mo	Liver mets	Supportive care	Bile duct cancer	Dead, 8.4 mo
69/M	Branch	Enucleation	HGD	(−)	36.7 mo	Lung mets	Supportive care		Alive, 46.2 mo
67/F	Branch	PPPD	HGD	(−)	13.4 mo	Remnant pancreas mass	Chemotherapy		Dead, 24.1 mo
61/M	Mixed	Distal	HGD	(+), IGD	84.3 mo	Remnant pancreas IPMN	Op refuse		Alive, 98.6 mo
61/M	Mixed	Total	HGD	(−)	29.4 mo	Peritoneal seeding	Supportive care		Dead, 32.4 mo
62/M	Main	Distal	HGD	(−)	90.4 mo	Remnant pancreas IPMN	Palliative HJ		Alive, 107.3 mo

EGC indicates early gastric cancer; HGD, high-grade dysplasia; HJ, hepaticojejunostomy; IGD, intermediate-grade dysplasia; IPMC, intraductal papillary mucinous carcinoma; LGD, low-grade dysplasia; PPPD, pylorus-preserving pancreaticoduodenectomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

TABLE 5. Recurrences That Required Surgical Treatment

Age/Sex	Initial IPMN Type	Initial Operation	Initial Pathology	Initial Resection Margin	DFS	Treatment	Final Status
55/M	Branch	Distal	IGD	(+)	55.6 mo	Remnant total → IPMC T3N0	Alive, 155.3 mo
41/M	Main	Distal	IGD	(−)	40 mo	Remnant total → IPMC T2N0	Alive, 72.6 mo
62/M	Main	Distal	HGD	(+)	90.4 mo	Palliative HJ	Alive, 107.3 mo
61/M	Mixed	Distal	HGD	(+)	84.3 mo	Refused operation	Alive, 98.6 mo
68/F	Branch	Ampullectomy	Minimally invasive	(−)	30 mo	PPPD → IPMC T1N0	Alive, 27.1 mo
64/M	Main	Distal	Invasive	(−)	11.5 mo	Supportive treatment due to comorbidity	Alive, 28.2 mo
47/F	Branch	Distal	Invasive	(−)	52.7 mo	Remnant total → PDAC T3N1	Alive, 120.1 mo
70/F	Main	PPPD	Invasive	(−)	24 mo	Remnant total → IPMC T3N0	Alive, 26.6 mo

HGD indicates high-grade dysplasia; HJ, hepaticojejunostomy; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia; PPPD, pylorus-preserving pancreaticoduodenectomy.

TABLE 6. Clinicopathologic Factors Related to Recurrence

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >65 yr	1.095	0.563–2.128	0.790			
Sex	0.703	0.361–1.372	0.302			
CEA >5 ng/mL	1.839	0.236–14.313	0.561			
CA19-9 >37 U/mL	4.583	2.216–9.479	<0.001	2.011	0.877–4.614	0.099
Dysplasia (vs LGD, IGD)			<0.001			
HGD	3.738	1.286–10.867	0.015	3.872	1.257–11.928	0.018
Invasive IPMN	12.420	5.538–27.854	<0.001	10.585	4.166–26.894	<0.001
IPMN type			0.012			
Main duct and mixed	2.175	1.111–4.256	0.023	0.815	0.365–1.823	0.619
Resection margin	1.184	0.496–2.828	0.704			

CA19-9 indicates cancer antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HGD, high-grade dysplasia; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia; OR, odds ratio.

most important predictor of disease recurrence (Table 6), with the odds ratio increasing as the degree of dysplasia increased.

DISCUSSION

The natural history of patients with IPMN after pancreatectomy has not been widely studied. Recurrence rates after surgical treatment have been reported to range from 0% to 12.9% in patients with noninvasive IPMN[5,8,16–19] and from 12.1% to 100% in patients with invasive IPMN,[5,8–10,17,19] with much of these variations due to the number of included patients and the length of follow-up. Recurrences may be locoregional, including in the remnant pancreas, to liver, lung, and peritoneal metastases. Previous studies, however, assessed IPMN recurrence as part of survival analyses, with fewer studies focusing on the recurrence pattern of IPMNs as the main issue. Because recurrence rate and recurrence pattern after resection of noninvasive IPMNs are important in determining postoperative surveillance targets and length of follow-up, it is necessary to analyze recurrence according to the pathologic grade of dysplasia. Moreover, although the risk of malignancy is higher in main duct–type IPMNs than in other IPMN types, no study to our knowledge has evaluated recurrence pattern or postoperative surveillance strategy according to IPMN type.

This study included a large prospective cohort of patients who underwent surgical treatment of pancreatic IPMNs and were followed up for a long time. We found that recurrence rate increased and DFS decreased as the degree of dysplasia increased, indicating that postoperative surveillance or treatment strategy should depend on the initial pathologic grade of dysplasia. Moreover, patients with high-grade dysplasia had a significantly higher recurrence rate and a significantly lower DFS rate than for patients with low- or intermediate-grade dysplasia. It is interesting to note that patients with high-grade dysplasia had lower survival rate, although it was a noninvasive tumor. Possibility of false-negative diagnosis missing small microinvasive foci, early metastatic activity of high-grade dysplasia as in breast,[20] colon,[21] or esophageal[22] in situ carcinoma, and development of multifocal dysplasia in the background of IPMN should be considered. At any rate, these findings indicate that patients with biopsy-proven high-grade dysplasia should undergo more intense postoperative surveillance than those with low- or intermediate-grade dysplasia. Ten of the 253 patients (4.0%) with low- or intermediate-grade dysplasia experienced recurrences, 2 as IPMNs requiring remnant total pancreatectomy 40 and 56 months after the initial operation. More importantly, one patient had an unresectable pancreatic cancer and 3 patients had liver metastases or peritoneal seeding after

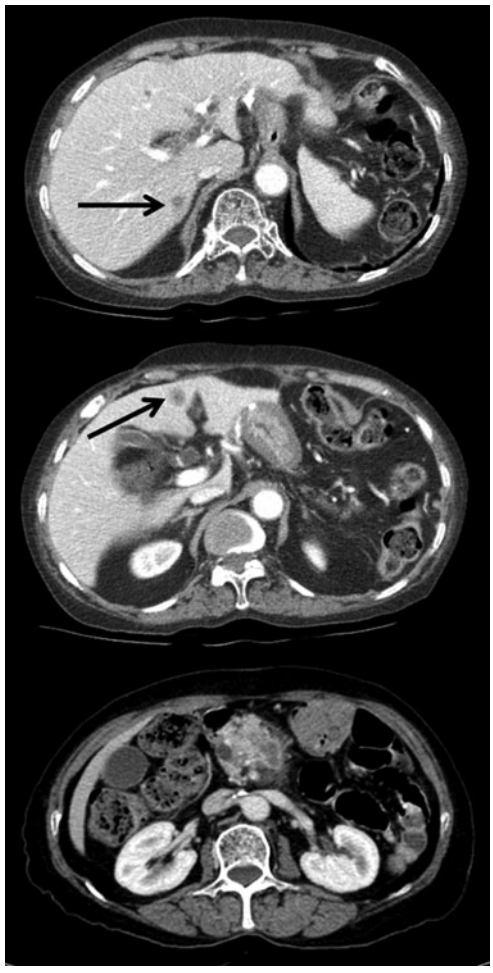

FIGURE 2. Recurrence after resection of benign IPMN in forms of unresectable pancreatic body cancer with liver metastasis. The arrows indicate liver metastasis.

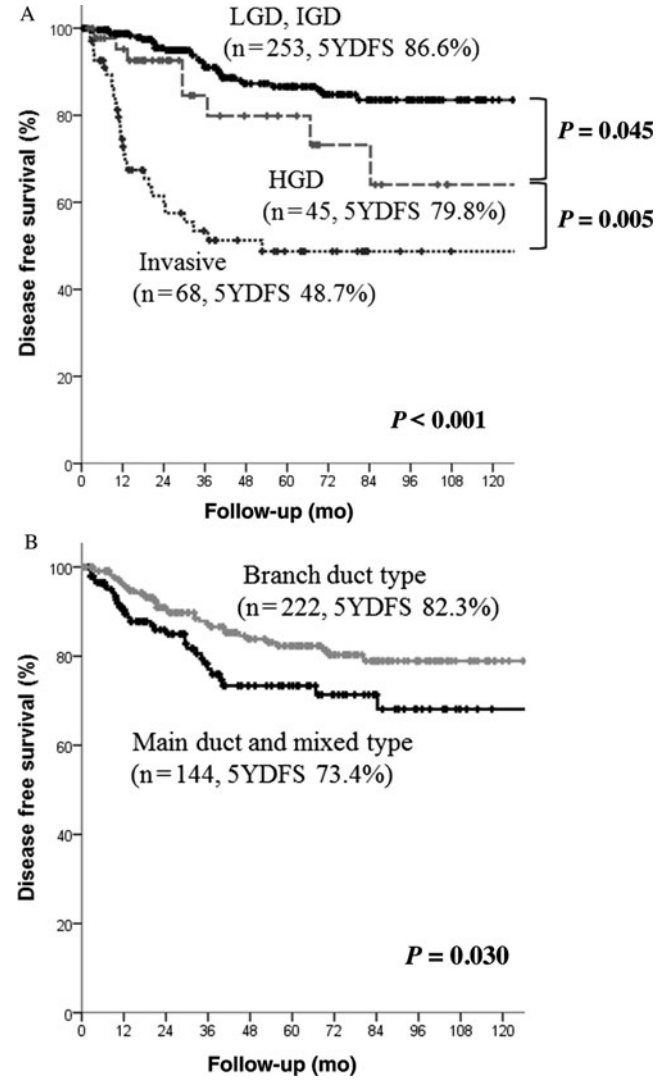

FIGURE 3. DFS after pancreatectomy for IPMN. A, DFS according to initial pathology. B, DFS according to initial IPMN type. HGD indicates high-grade dysplasia; IGD, intermediate-grade dysplasia; LGD, low-grade dysplasia; 5YDFS, 5-year disease-free survival.

35 to 69 months. For these patients, there is a possibility of undetected concurrent PDAC at the time of operation for IPMN or development of metachronous ductal adenocarcinoma among patients with initially noninvasive IPMN. Although referring the situations as "disease recurrence" can be inappropriate, these findings indicate that even patients with low- or intermediate-grade dysplasia should undergo postoperative surveillance for at least 5 years to monitor for any evidence of disease recurrence or development of a new pancreatic cancer.

Although most previous studies did not assess the relationship between IPMN type and recurrence, one found an association[5] whereas another did not.[18] In this study, IPMN type was correlated with the DFS rate, but multivariate analysis revealed that there was no correlation between IPMN type and recurrence rate. Degree of dysplasia was more important than IPMN type. However, the rate of recurrent IPMN in the remnant pancreas requiring surgical treatment was higher in main duct–type IPMNs and IPMNs involving main pancreatic duct had more frequent peritoneal seeding than branch duct–type IPMNs. Therefore, postoperative surveillance of patients with IPMNs involving main pancreatic duct should include closer monitoring of the remnant pancreas and peritoneal metastasis.

Although previous studies have suggested that invasive cancer,[5–7] cancer antigen 19-9,[6] and lymphadenopathy[7] are risk factors for the recurrence of IPMN, our study found that the degree of dysplasia was the most important risk factor, with the odds ratio increasing with increasing degree of dysplasia. The impact of resection margin is also unclear, with some studies suggesting that resection margin was not correlated with disease recurrence[23–26] whereas others found that positive resection margin was associated with disease recurrence or poor survival outcomes.[18,27] Noninvasive pathology of the resection margin did not increase the risk of recurrence.[23,25,26] In our study, 7 of the 65 patients (10.8%) with positive resection margins had recurrences, but this rate was not higher than that in patients with negative resection margins. Our study cohort included only one patient with a positive resection margin with high-grade dysplasia, and this patient did not experience disease recurrence after 86 months of follow-up. We found that resection margin status was not statistically correlated with recurrence.

Finally, studies have emphasized the necessity for total pancreatectomy,[7,8] based on the theory of field cancerization of IPMN.[28] However, we found that, compared with partial pancreatectomy, total pancreatectomy did not decrease the risk of recurrence, a finding in agreement with previous results.[9] Moreover, total pancreatectomy has adverse metabolic consequences and reduces quality of life. Therefore, we do not recommend prophylactic total pancreatectomy to prevent disease recurrence.

CONCLUSIONS

Our analysis of 366 consecutive patients who underwent surgical treatment of IPMN found that the overall recurrence rate was 10.7% and the median DFS was 41.1 months. Recurrence rate was positively correlated with a higher grade of dysplasia, especially being higher in patients with high-grade dysplasia than in those with low- or intermediate-grade dysplasia. Locoregional recurrences and liver, lung, and peritoneal metastases occurred more frequently in patients having tumors with invasive IPMN than noninvasive IPMN. IPMN type had no effect on the recurrence rate after multivariate analysis, whereas peritoneal seeding was more frequent in patients with IPMN involving main pancreatic duct–type IPMN than branch duct–type IPMN. Of the 298 patients with noninvasive IPMN, 16 patients, including 3 with low-grade dysplasia, 7 with intermediate-grade dysplasia, and 6 with high-grade dysplasia, experienced recurrences, and 12 of them were IPMNs requiring surgical treatment, pancreatic cancer, locoregional recurrence, or disseminated metastases that required further treatment. The overall 5-year DFS rate of all patients was 78.9%. Patients with invasive IPMN had the worst prognosis, followed by patients with high-grade dysplasia and low- to intermediate-grade dysplasia. The DFS rate was significantly lower for patients with high-grade dysplasia than for low- to intermediate-grade dysplasia. IPMNs involving main pancreatic duct had the lower DFS rate than those with branch duct–type IPMN. However, multivariate analysis showed that the degree of dysplasia was the most important predictor or recurrence. Positive resection margin or partial pancreatectomy did not increase recurrence rate.

In addition, IPMN recurrence rate was related to the initial pathologic grade of dysplasia, and 5.4% of benign or noninvasive IPMNs have recurrence including distant metastasis. Patients with high-grade dysplasia had a significantly higher rate of recurrence and a lower DFS rate than patients with low- to intermediate-grade dysplasia. These findings indicate the need for postoperative surveillance, even in patients with benign or noninvasive tumors, for at least 5 years, with patients having high-grade dysplasia requiring more frequent surveillance. The recurrence rate and prognosis are comparable in patients with invasive IPMN and those with PDAC, suggesting that patients with these 2 conditions should undergo similar monitoring.

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