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Pancreaticojejunostomy with Invagination of the Punched Pancreatic Remnant After Medial Pancreatectomy and Enucleation for Multiple Metastases of Renal Cell Carcinoma: Report of a Case

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Abstract
We report the successful resection of multiple pancreatic metastases of renal cell carcinoma (RCC), achieved by performing medial pancreatectomy and enucleation, preserving as much of the pancreatic parenchyma as possible. Most of the distal remnant pancreas was placed into the jejunal lumen and all three cut surfaces were covered to prevent pancreatic leakage. The postoperative course was uneventful, without any sign of pancreatic fistula. The patient is well without any evidence of recurrence or impairment of exocrine or endocrine pancreatic functions 1 year after surgery. Considering the unusual behavior of RCC metastasis and the difficulty in predicting the pattern of recurrence, we should devise the optimal surgical strategy to provide cancer-free surgical margins and preserve as much of the pancreatic parenchyma as possible.

Key words Multiple pancreatic metastases · Renal cell carcinoma · Medial pancreatectomy · Pancreatic fistula

Introduction

Pancreatic metastases are often associated with diffuse systemic disease at the time of diagnosis, so pancreatic surgery is rarely indicated. However, solitary and multiple isolated pancreatic metastases from renal cell carcinoma (RCC) are potentially manageable by radical surgery, because of their slow growth pattern and potentially positive outcome.[1–3] The effectiveness or palliation of pancreatic resection for metastatic RCC in selected patients has been reported,[1–3] but the appropriate procedures for pancreatic resection are poorly documented, especially for multiple metastatic lesions.[3–6] Not only the indications for pancreatectomy but also the types of surgical procedure are a major clinical concern. The precise detection of tiny hypervascular pancreatic metastatic lesions, using multidetector-row computed tomography,[7] and improved postoperative morbidity after procedures such as medial pancreatectomy[8,9] have made atypical resections possible in patients with multiple pancreatic metastases from RCC.[2]

We report a case of multiple pancreatic metastases from RCC, treated successfully by medial pancreatectomy and enucleation of two metastatic lesions, instead of a radical pancreatectomy. A pancreaticojejunostomy was performed with invagination of the punched remaining pancreas to prevent a postoperative pancreatic fistula after this atypical pancreatectomy.

Case Report

The patient was a 54-year-old man who had undergone a right nephrectomy for RCC 10 years earlier. He was referred to us after a follow-up abdominal computed tomography (CT) revealed a pancreatic tumor in the pancreatic neck without any specific symptoms. Multidetector-row CT demonstrated three hypervascular tumors in the neck (T1: 30 mm in diameter) and tail (T2: 7 mm in diameter and T3: 10 mm in diameter) of the pancreas (Fig. 1A–C). Ultrasonography showed slight dilation of the distal part of the main pancreatic duct (MPD; Fig. 1D). There was no evidence of local recurrence of the RCC or extrapancreatic metastatic spread. Laboratory findings were all within normal limits, including the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels. Glucose tolerance was also normal and the hemoglobin A_{1c} (HbA_{1c}) percentage was 4.7% (normal range <5.6%). We performed medial pancreatectomy with enucleation

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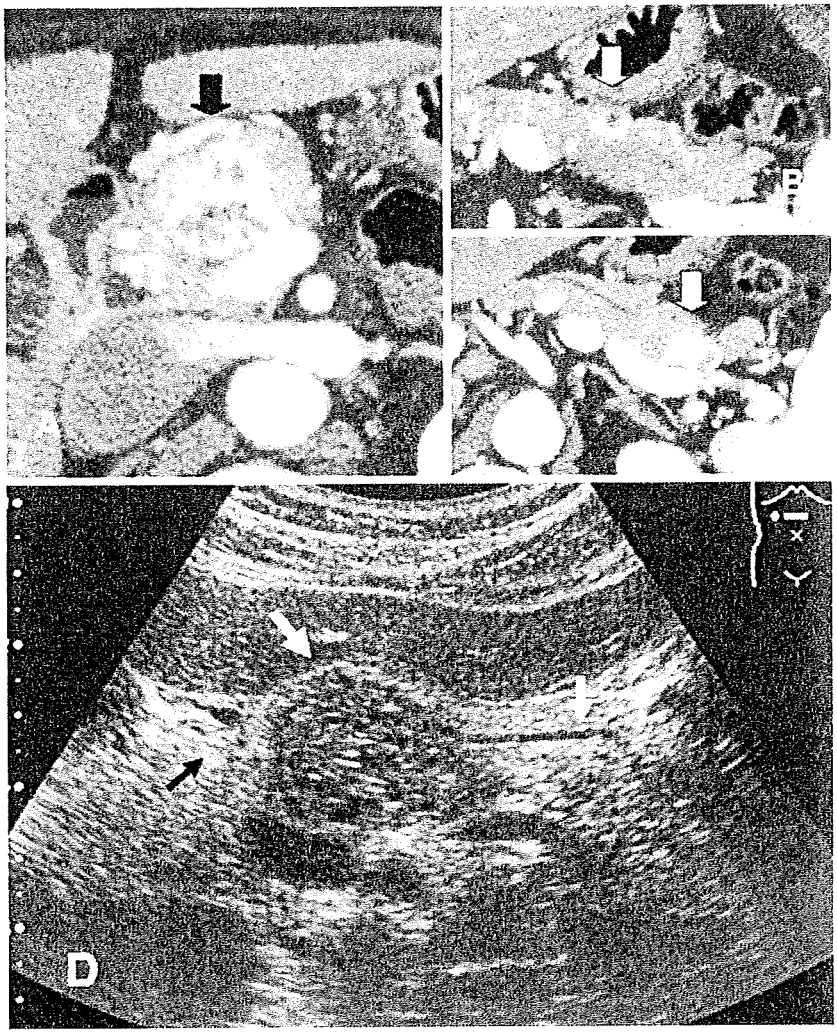

Fig. 1. Multidetector-row computed tomography (MDCT) showed **A** a 30-mm hypervascular tumor in the pancreatic neck (T1; *black arrow*); **B** a 7-mm tumor in the pancreatic tail (T2; *white arrow*); and **C** a 10-mm hypervascular tumor in the pancreatic tail (T3; *white arrow*). **D** Abdominal ultrasonography showed a round and heterogeneous echoic mass, 30 mm in diameter, with slight dilation of the main pancreatic duct (*white arrows*); the *black arrow* indicates the gastroduodenal artery

of two metastatic lesions, to preserve as much pancreatic exocrine and endocrine function as possible.

Surgical Procedure

Intraoperative ultrasonography was performed to identify all the nodules, to define the relationships between the nodule and MPD, and to establish the appropriate resection line. A T1 tumor was located about 5 mm distal from the gastroduodenal artery, adjacent to the MPD. A T2 tumor and a T3 tumor were located about 50 mm and 30 mm proximal from the splenic hilum, respectively. Both tumors were near the MPD. After dissecting and mobilizing the pancreatic neck, body, and tail from the surrounding tissue, we performed a medial pancreatectomy for the T1 tumor. The pancreatic parenchyma was transected using a Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) with sufficient proximal and distal margins from the T1 tumor. The proximal side of the MPD was ligated and cut, and the proximal stump of the pancreas was sewn in a fish-mouth shape. We then enucleated the T2 and T3 tumors using the Harmonic scalpel. Enucleation was done to excise the affected parenchyma with a minimal resection margin. A 4-F stent tube (Suikan tube, Sumitomo Bakelite, Tokyo, Japan) was inserted into the MPD of the distal remnant pancreas (Fig. 2A). We divided the jejunum with a linear stapler and then made a jejunal loop. A small incision was made in the lateral wall of the jejunal loop and the distal remnant pancreas was put into the jejunal lumen (Fig. 2B). The three cut surfaces of the pancreatic parenchyma were all covered within the jejunal lumen. Once the pancreas was in place, a row of interrupted 4-0 absorbable sutures was applied circumferentially to secure the edge of the jejunal cuff to the pancreas, and an end-to-side pancreaticojejunostomy was made. The pancreatic tube was connected to a drainage bottle in a closed fashion.

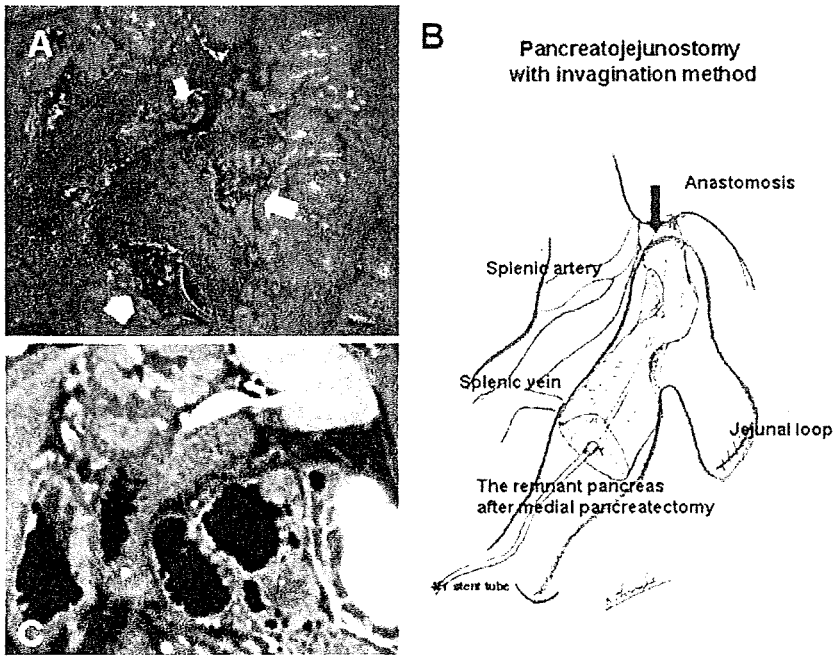

Fig. 2. **A** The *arrowhead* indicates the cut surface after the medial pancreatectomy with a 4-F stent tube. The *white arrows* indicate the row surfaces after enucleation of the two metastatic lesions. **B** Schematic illustration of the invagination method. The *black arrow* indicates the anastomosis. **C** MDCT showed the invaginated remnant pancreas, 2 months after the operation

Pancreatic juice was drained continuously through the tube for 2 weeks. We measured the amylase concentration of the collected fluid from a peripancreatic drain inserted near the anastomosis.

The intraoperative blood loss was 170 ml and the operative time was 284 min. Histologically, all of the tumors were surrounded by a fibrous capsule separating them distinctly from the normal pancreas. This tumor consisted of cells arranged in trabecular structures with clear granular cytoplasm; these findings were compatible with metastatic RCC. All surgical margins were negative for cancer cells, and no metastases were found in the dissected peripancreatic lymph nodes.

The patient had an uneventful postoperative course, without any sign of pancreatic leakage, and he was discharged on day 18. Multidetector-row CT done 2 months later showed the invaginated remnant pancreas (Fig. 2C). The patient was well without any evidence of recurrence 1 year after surgery. His body weight was the same as before surgery, he did not complain of any symptoms of pancreatic exocrine insufficiency such as diarrhea, and the HbA_{1c} level was 5.0%. Normal glycemia has also been maintained without medication and he has not needed oral enzyme supplements.

Discussion

Even in the presence of multiple pancreatic metastases or extrapancreatic metastatic sites, the resection of pancreatic metastases from RCC has been advocated in selected patients because of the unusually positive outcome.[2,3] Table 1 shows the clinical characteristics of 12 consecutive patients with pancreatic metastases from RCC, surgically treated at the National Cancer Center Hospital between January 1988 and December 2007, including the subject of this case report. Six (50%) patients had multiple metastases; four (33%) had undergone previous surgery for extrapancreatic metastases before the pancreatectomy; and seven (58%) had extrapancreatic metastases after the pancreatectomy. None of the patients in this series, including the 3 who had multiple pancreatic metastases and did not undergo a total pancreatectomy, have suffered local or pancreatic recurrence in the remnant pancreas. Three patients (25%) died of disease, two (16%) are alive with recurrent disease, and eight (75%) are alive with no evidence of disease. This suggests that aggressive or prophylactic resection might be unnecessary, because the behavior of metastatic RCC is difficult to predict and pancreatic metastases have been mistaken as localized disease due to their slow-growing and indolent nature. According to Zerbi et al.,[3] the choice of a standard or an atypical surgical procedure is probably less important than an accurate search for multiple pancreatic lesions. We performed a medial pancreatectomy with enucleation of two lesions instead of a total or distal pancreatectomy for multiple pancreatic metastases from RCC, to preserve the endocrine and exocrine pancreatic function.

The mechanism of metastasis of RCC to the pancreas is still unclear. While hematogenous systemic spread is possible, peripancreatic lymph node involvement with pancreatic metastases is considered to be rare.[1,2] Sellner

Table 1. Operative procedures and outcome of 12 patients with pancreatic metastases from renal cell carcinoma surgically treated at the National Cancer Center Hospital between 1988 and 2007

Case no.	Age (years)/Sex	Site (RCC)	Interval (months)	Metastases before pancreatectomy	Tumor number	Operation	Recurrence after pancreatectomy	Management of recurrence	Follow-up time (months)	Outcome
1	60/M	Right	41	—	4	TP	—	—	240	NED
2	47/F	Left	55	—	7	TP	Thyroid	Resection	169	NED
3	66/M	Right	209	Lung/Lymph nodes	1	DP	Lung/Lymph node	No treatment	89	AWD
4	81/F	Right	363	—	5	PPPD	Liver	No treatment	12	DOD
5	58/M	Right	142	Lung	2	TP	Lung/Bone/Liver	No treatment	63	DOD
6	61/F	Right	136	—	1	PPPD	—	—	66	NED
7	62/M	Right	81	—	1	DP	Lung	No treatment	56	AWD
8	50/M	Left	21[a]	Lung	1	Completion TP	Right kidney/Lung	Partial nephrectomy/ Pneumonectomy	51	NED
9	70/F	Right	90	—	1	DP	—	—	41	NED
10	73/F	Left	243	Lung/Pituitary	1	PPPD	Liver/Pituitary	No treatment	17	DOD
11	64/F	Left	19[b]	—	4	DP	—	—	15	NED
12	54/M	Right	122	—	3	MP/Partial resections	—	—	12	NED

RCC, renal cell carcinoma; TP, total pancreatectomy; DP, distal pancreatectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; MP, medial pancreatectomy; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease

[a] Pancreatic lesions were detected synchronously at the time of nephrectomy. Distal pancreatectomy with left nephrectomy was performed; pancreatic head lesion was not resected, but treated with interferon-α chemotherapy

[b] Pancreatic lesions were detected synchronously at the time of nephrectomy. Interferon-α chemotherapy was performed

et al.[2] hypothesized that RCC has a high affinity for the parenchyma of the pancreas, and that only this location provides the conditions it needs to mature and manifest metastases. However, this explanation of the behavior of metastatic RCC might not justify prophylactic radical resections in all patients. Total pancreatectomy used to be generally accepted for multiple scattered metastases, but taking metastatic mechanisms into consideration, the parenchyma should be preserved if complete extirpation with a free margin is possible. Oncologically, hematogenous systemic metastases might develop in any extrapancreatic organs, and there are no clear data supporting completion pancreatectomy or radical pancreatectomy including regional lymph node dissection.

A pancreatic fistula might form from the cut surface after partial resection of two metastatic lesions on the distal side of the pancreatic remnant following such an atypical resection. To prevent pancreatic leakage from the three cut surfaces, we inserted almost all of the distal remnant pancreatic parenchyma into the jejunal lumen and covered all the cut surfaces. A pancreaticojejunostomy using the invagination method is thus recommended, especially for patients with a normal pancreas, to prevent stenosis of the pancreatic duct opening.[10] After conventional pancreaticojejunostomy with a duct-to-mucosa anastomosis, there is a possibility of stricture of the anastomosis, which would lead to exocrine and endocrine insufficiency. However, anastomotic stricture does not tend to occur with the invagination technique because there is no pancreaticojejunal anastomosis, although it is still necessary to survey the long-term efficiency of this procedure. Although the distal remnant pancreas was mobilized from its surrounding attachments and splenic vessels, an enhanced CT scan done 2 months after the operation showed sufficient blood flow of the pancreatic parenchyma.

In summary, we describe how we resected multiple pancreatic metastases from RCC, by performing a medial pancreatectomy and enucleation, preserving as much of the pancreatic parenchyma as possible. Although it is difficult to predict the pattern of recurrence after such an atypical pancreatectomy, Bassi et al.[5] reported 29% pancreatic recurrence after a distal pancreatectomy in two patients and after an atypical resection in three. Thus, we must take care not to overlook recurrence in the remnant parenchyma, although should a recurrent lesion appear in either the proximal or distal remnant pancreas, it would still be possible to avoid total pancreatectomy.

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Clinical Significance of Frozen Section Analysis During Resection of Intraductal Papillary Mucinous Neoplasm: Should a Positive Pancreatic Margin for Adenoma or Borderline Lesion Be Resected Additionally?

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BACKGROUND: The clinical significance of a positive intraoperative frozen section analysis of the pancreatic margin, especially for adenoma or borderline lesion, is not well understood during operations for intraductal papillary mucinous neoplasm of the pancreas.

STUDY DESIGN: Data from 130 consecutive patients who underwent intraductal papillary mucinous neoplasm resection in a single institution were retrospectively analyzed.

RESULTS: In the first intraoperative frozen section analysis, 26 patients were positive for adenoma or borderline lesion, 10 for carcinoma in situ, 2 for cancer cells floating in the duct, and 6 for invasive cancer. Twenty-nine patients underwent additional resection, and 105 patients finally achieved a negative pancreatic margin. Among 18 patients with a positive pancreatic margin for adenoma or borderline lesion, only 1 had a recurrence. All 20 patients who suffered a recurrence harbored invasive intraductal papillary mucinous carcinoma in resected specimens. In multivariate analysis, predictive factors of recurrence after intraductal papillary mucinous carcinoma resection were the presence of lymph node metastasis, serosal invasion, and a high level of serum carbohydrate antigen 19-9.

CONCLUSIONS: The presence of adenoma or borderline lesion at the pancreatic margin does not always warrant further resection because of the low recurrence rate in the remnant pancreas. Recurrence after intraductal papillary mucinous neoplasm resection is influenced primarily by the presence and extent of invasive cancer rather than the status of the pancreatic margin. (J Am Coll Surg 2009; 209:614–621. © 2009 by the American College of Surgeons)

The reported incidence of intraductal papillary mucinous neoplasm (IPMN) has been increasing in recent years, and its biologic behavior has been progressively elucidated.[1-6] IPMN is characteristic of papillary proliferation and prominent mucin production, resulting in marked dilatation of branch or main pancreatic ducts (MPD), or both. Those features are reflected in the radiologic appearance of IPMN, making the diagnosis easy in typical cases. But the margin of IPMN is not always associated with such characteristic findings and often shows gradual transmission from low-grade atypia to normal epithelium without marked ductal dilatation or papillary projections detectable on imaging examinations. So, pre- or intraoperative assessment of tumor spread is often difficult and incorrect. To secure a tumor-free margin, intraoperative frozen section analysis (IOFSA) of the pancreatic cut margin is indispensable, at the same time preserving the largest possible pancreas remnant during resection of IPMN.[7-9] International consensus guidelines for management of IPMN also advocate the importance of IOFSA.[10] But the relative risk and biologic significance of various grades of IPMN at the pancreatic margin are not fully established, especially for those

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Abbreviations and Acronyms

HD = high-grade dysplasia
IC-IPMC = invasive cancer originating in IPMC
IOFSA = intraoperative frozen section analysis
IPMC = intraductal papillary mucinous carcinoma
IPMN = intraductal papillary mucinous neoplasm
LD = low-grade dysplasia
MD = moderate dysplasia
MI-IPMC = minimally invasive intraductal papillary mucinous carcinoma
MP = middle pancreatectomy
MPD = main pancreatic duct
TP = total pancreatectomy

with adenoma or borderline lesions. In this retrospective study, we analyzed the result of IOFSA and the incidence and loci of recurrence after IPMN resection. We also investigated the rational criteria for additional pancreatic resection during surgery for IPMN.

METHODS

From 1986 to 2007, 130 cases of IPMN were resected at the National Cancer Center Hospital in Tokyo. Except for 3 patients who underwent 1-step total pancreatectomy for IPMNs diffusely involving the entire pancreas, 127 patients underwent IOFSA of the pancreatic margin. We have been performing IOFSA routinely and making it a rule to manage pancreatic margins as follows: (1) negative (normal epithelium) or hyperplasia, no further resection; (2) positive for adenoma (low-grade dysplasia [LD]) or borderline lesion (moderate dysplasia [MD]), no more resection or additional resection in some cases, but total pancreatectomy is avoided; and (3) positive for carcinoma in situ (CIS or high-grade dysplasia, [HD]) or invasive cancer, additional resection including total pancreatectomy if necessary. In cases of LD or MD, the decision to do additional resection was made by the individual surgeon, depending on the site of the first pancreatic transection and the patient's general condition, including age, comorbidity, and compliance. Generally, to secure the safety of the pancreatoenteric anastomosis and postoperative glucose tolerance, the limit of additional pancreatic resection was considered to be just beneath the gastroduodenal artery in a left-sided pancreatectomy and 3 to 5 cm to the left side of the superior mesenteric artery in a right-sided pancreatectomy. The amount and extent of the lesions on the frozen section were also taken into consideration. According to information from pathologists, surgeons tended to perform additional resections, when feasible, for frozen sections with massive papillary proliferation or with widespreading lesions both into small branch ducts and the MPD, even if the cellular atypia in the lesion was LD or MD.

In the first IOFSA, the pancreatic margin was cut by a pathologist immediately after the specimen was retrieved from the operative field. The margin tissue was embedded in optimal cutting temperature compound (Sakura Finetek) and frozen in acetone cooled with dry ice. The 5-μm thick tissue sections cut by a cryostat (OTF5000; Bright Instrument Co Ltd) were fixed in 18% formalin with 50% ethanol, stained with hematoxylin and eosin, and immediately analyzed by more than 2 pathologists. Substantial care was taken not to touch a pancreatic stump directly in order to avoid epithelial abrasion. To ensure a freshly cut surface, the pancreas was sometimes transected at the final step of the operative procedure, or, in other cases, the pancreatic stump was secured by a surgeon immediately after the pancreas transection in the operative field. If there was difficulty in making a diagnosis, another deeper section was cut to help with the diagnosis. In an additional resection, the pancreatic stump was dissected from the surrounding retroperitoneal tissues or vessels, and 1 to 2 cm of pancreas was resected by surgical scalpel. Again, the greatest possible effort was exerted not to damage the stump.

After the IOFSA, all the margin tissues were fixed in 10% formalin and embedded in paraffin. Sections 3 μm in thickness were cut from the block, stained with hematoxylin and eosin, and analyzed for the definitive diagnosis on a subsequent day.

Patients were followed up on an outpatient basis every 3 to 6 months after operation. Postoperative examinations included a CT scan, ultrasonography, and blood test with measurement of CEA and carbohydrate antigen 19-9 (CA 19-9). The time and site of initial tumor recurrence were recorded based on radiologic findings, even if the patient did not undergo a biopsy. CT and ultrasonography were conducted when recurrence was suspected, and both studies were used to complement each other. When progression of the disease was confirmed by repeated imaging studies, the date of recurrence was deemed to be the date of the first detection of a suspicious lesion.

Statistical analysis

Comparisons of categoric variables were performed using the chi-square test. Recurrence rates were calculated by the Kaplan-Meier method. Univariate analysis was performed for predictive factors of recurrence using the log-rank test. Factors found significant by univariate analysis were subjected to multivariate analysis using the backward elimination method of the Cox proportional hazards model. Differences at $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 11.0J software (SPSS, Inc).

Table 1. Pathologic Diagnosis of Pancreatic Margin

Diagnosis	Initial IOFSA		Additional resection		Final IOFSA*		Definitive diagnosis on HE	
	n	%	n	%	n	%	n	%
Negative	83	65	0	0	106	83	105	83
LD or MD	26	20	12	46	19	15	18	14
HD (CIS)	10	8	10	100	0	0	1	1
Cancer cells floating in duct	2	2	1	50	1	1	1	1
Invasive cancer	6	5	6	100	0	0	1	1
Epithelium denuded	0	0	0	0	1	1	1	1
Total	127		29	23	127		127	

*Identical to results of the first IOFSA for patients who did not undergo additional resection.
CIS, carcinoma in situ; HD, high-grade dysplasia (carcinoma in situ); HE, hematoxylin and eosin stain; IOFSA, intraoperative frozen section analysis; LD, low-grade dysplasia (adenoma); MD, moderate dysplasia (borderline lesion).

RESULTS

The median age of the patients was 67 years (range 40 to 84 years) and the male/female ratio was 76/54. Macroscopically, 55 IPMNs were classified as branch type, 30 as MPD type, and 45 as mixed type. Pathologically, 22 IPMNs were diagnosed as adenomas (LD), 13 as borderline lesions (MD), 26 as noninvasive intraductal papillary mucinous carcinoma (IPMC) (carcinoma in situ, HD), and 69 as invasive IPMCs, according to the classification of the World Health Organization (WHO)[11] and the Armed Forces Institute of Pathology (AFIP).[12] The lesion was graded by the highest degree of atypia in the entire IPMN. Invasive IPMCs were further classified as 35. minimally invasive IPMCs (MI-IPMC) and 34 invasive carcinomas originating in IPMCs (IC-IPMC), based on the classification of the Japan Pancreas Society[13] and the pathologic diagnostic criteria described in detail previously.[14]

Operative procedures consisted of 9 pancreatoduodenectomies (PD), 70 pylorus-preserving pancreatoduodenectomies, 1 pylorus-preserving pancreatoduodenectomy + distal pancreatectomy (DP), 34 DPs, 10 middle pancreatectomies (MP), and 6 total pancreatectomies (TP). Procedures were categorized into pancreatoduodenectomy, DP, TP, and MP groups for the following analysis. Three patients underwent one-step TP as planned preoperatively; the other three patients underwent TP as a result of additional resection for positive pancreatic margin.

Results of intraoperative frozen section analysis

At the initial IOFSA, 83 margins were interpreted as negative (normal epithelium or hyperplasia); 26 margins with LD or MD; 10 margins with HD, CIS; 2 margins with cancer cells floating in the pancreatic duct; and 6 margins with invasive cancer (Table 1). No patients with negative margins underwent additional pancreatic resection, but 12 of the 26 patients with LD or MD, 10 of the 10 patients with HD, 1 of the 2 patients with cancer cells floating in the pancreatic duct, and 6 of the 6 patients with invasive cancer underwent additional resections. One patient with cancer cells floating in the pancreatic duct did not undergo additional resection, because the epithelium of the pancreatic duct was negative for tumor extension. Additional resection was performed once in 24 patients, twice in 4 patients, and 3 times in 1 patient. In the final IOFSA among the 29 patients who underwent additional resection, 23 margins were diagnosed as negative and 5 margins with LD or MD. In the one remaining patient, the epithelium of the duct was completely denuded and impossible to diagnose. This patient did not undergo more resection, because there was no evidence of invasive cancer in the pancreatic parenchyma and the further resection was difficult after two previous additional resections. Regarding the definitive diagnosis of the formalin-fixed sections, 1 margin interpreted as negative on IOFSA was finally diagnosed as positive for neural invasion, and 1 margin with MD was finally diagnosed as HD (Table 1). As a result, the concordance rate between IOFSA and the definitive diagnosis was 98%.

The positive rate in initial IOFSA was compared among categories of the pathologic diagnoses, operative procedures, and macroscopic types (Table 2). The positive rate of atypia more than LD (adenoma) was significantly high in the TP and MP groups ($p = 0.003$). The positive rate of atypia more than HD (carcinoma in situ) was significantly high in patients with MI-IPMC and IC-IPMC ($p < 0.001$), in the TP and MP groups ($p < 0.001$), and in patients with MPD and mixed type IPMN ($p = 0.011$). The positive rate for invasive cancer was significantly high in patients with TP and MP ($p < 0.001$) and in patients with MPD and mixed type IPMN ($p = 0.025$). But after additional pancreatic resection, most of these significant differences disappeared, except that the positive rate for atypia more than HD was significantly high in patients with IC-IPMC ($p = 0.028$) (Table 2).

Table 2. Pancreatic Margin Status According to the Pathologic Diagnosis of the Entire Intraductal Papillary Mucinous Carcinoma, Operative Procedure, and Macroscopic Type

		Result of initial IOFSA				Result of definitive diagnosis			
Variable	n	Negative	Positive for atypia ≥ LD*	Positive for atypia ≥ HD*	Positive for invasive cancer	Negative†	Positive for atypia ≥ LD*	Positive for atypia ≥ HD*	Positive for invasive cancer
Pathologic diagnosis									
IPMA or borderline	35	26	9 (26)	0	0	30	5 (14)	0	0
Noninvasive IPMC	26	17	9 (35)	1 (4)	0	19	7 (27)	0	0
MI-IPMC	34	22	12 (35)	5 (15)	2 (6)	30	4 (12)	0	0
IC-IPMC	32	18	14 (44)	12 (38)	4 (13)	27	5 (16)	3 (9)	1 (3)
p Value (chi-square test)			0.492	< 0.001	0.06		0.433	0.028	0.393
Operative procedures									
PD group	80	59	21 (26)	6 (8)	1 (1)	69	11 (14)	1 (1)	0
DP group	34	21	13 (38)	6 (18)	1 (3)	27	7 (21)	2 (6)	1 (3)
TP group	3	0	3 (100)	3 (100)	2 (67)	3	0	0	0
MP group	10	3	7 (70)	3 (30)	2 (20)	7	3 (30)	0	0
p Value (chi-square test)			0.003	< 0.001	< 0.001		0.43	0.463	0.431
Macroscopic type									
Branch type	55	41	14 (26)	2 (4)	0	45	10 (18)	1 (2)	0
Mixed type	43	28	15 (35)	9 (21)	5 (12)	38	5 (12)	1 (2)	1 (2)
MPD type	29	14	15 (52)	7 (24)	1 (3)	23	6 (21)	1 (3)	0
p Value (chi-square test)			0.055	0.011	0.025		0.543	0.896	0.374

Numbers in parentheses are percents.
*Patients with cancer cells floating in the pancreatic duct are included.
†One patient with denuded epithelium is included.
DP, distal pancreatectomy; HD, high-grade dysplasia (carcinoma in situ); IC-IPMC, invasive cancer originating in intraductal papillary mucinous carcinoma; IOFSA, intraoperative frozen section analysis; IPMA, intraductal papillary mucinous adenoma; IPMC, intraductal papillary mucinous carcinoma; LD, low-grade dysplasia (adenoma); MI-IPMC, minimally invasive intraductal papillary mucinous carcinoma; MP, middle pancreatectomy; MPD, main pancreatic duct; PD, pancreatoduodenectomy; TP, total pancreatectomy.

Analysis of recurrence

All 130 patients were followed up after resection of IPMN for a median of 41 months (range, 1 to 210 months; mean, 50 months). Among 3 patients who underwent 1-step TP, 1 with IC-IPMC developed a recurrence in the lymph nodes 5.6 months after operation. Among 127 patients who underwent IOFSA, tumor recurrence was observed in 19 (15%), and 17 of the 19 were patients with negative pancreatic margins in definitive diagnosis (Fig. 1). Recurrence in the remnant pancreas was detected in two patients with negative pancreatic margins. They developed an MI-IPMC and an invasive ductal carcinoma in the pancreatic remnant, respectively, and underwent reoperation 38 and 50 months, respectively, after the first operation. Both patients are doing well, with no evidence of recurrence 24 and 43 months after the second operation, respectively. The other 15 patients with negative pancreatic margins developed recurrence in the peritoneum (n = 4), liver (n = 7), lung (n = 1), lymph nodes (n = 2), and local (n = 1) (Fig. 1). Two patients had MI-IPMCs, and 13 patients had IC-IPMCs. Among 18 patients with LD or MD in the definitive diagnosis of the pancreatic margin, 1 developed a lymph node recurrence. One patient with invasive cancer in the definitive diagnosis of the pancreatic margin developed a local recurrence. Both were patients with IC-IPMCs. The patients with cancer cells floating in the pancreatic duct, HD, and denuded epithelium at the pancreatic margin in definitive diagnosis developed no recurrences (Fig. 1). In summary, all 20 patients who developed a recurrence were patients with invasive IPMCs, and most of the recurrences occurred at distant locations.

Conversely, among 61 patients with a pathologic diagnosis of entire IPMN as adenomas (LD), borderline lesions (MD), or noninvasive IPMC (HD), none developed recurrences during a median followup time of 43 months (range, 5 to 158 months; mean, 55 months). In 35 patients with MI-IPMC during a median followup of 47 months (range, 10 to 210 months; mean, 57 months), 2 (6%) developed recurrences in the remnant pancreas, and both were surgically resected as mentioned previously. The other two patients developed multiple liver metastases, and one of them died from the disease. In 34 patients with IC-IPMC during a median followup of 24 months (range, 1 to 88 months; mean, 32 months), 16 (47%) developed recurrences, and 12 died from the disease.

Figure 2 compares recurrence rates among patients with noninvasive IPMC, MI-IPMC, and IC-IPMC. There was

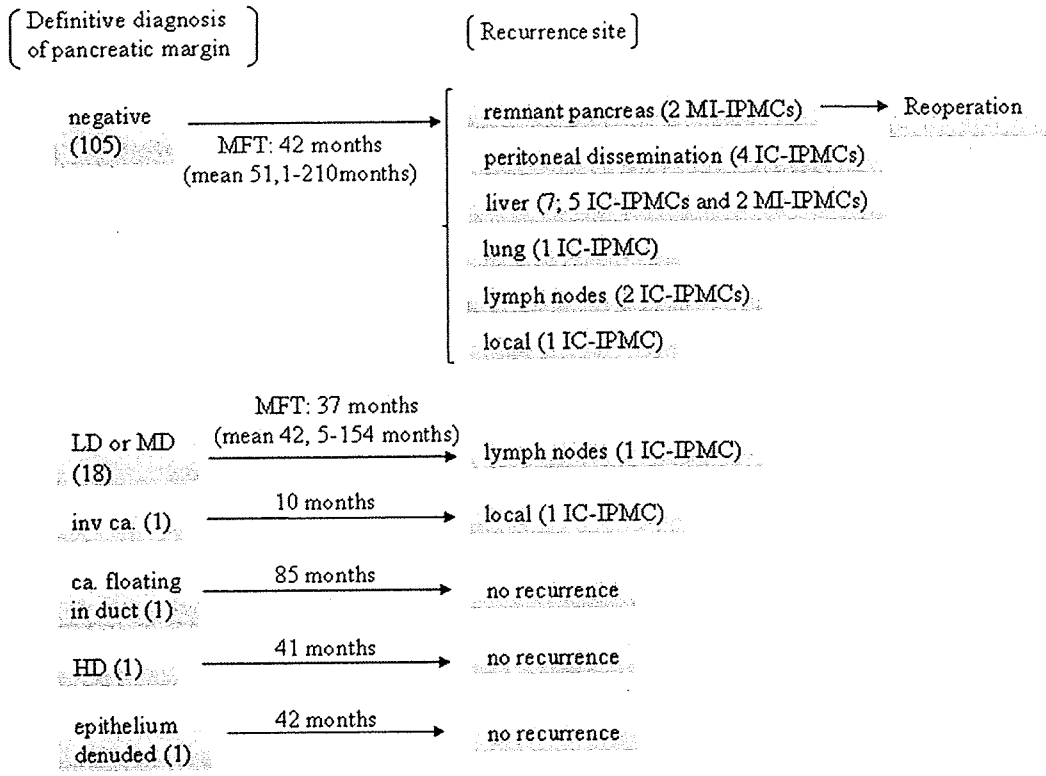

Figure 1. Recurrence sites after intraductal papillary mucinous neoplasm resection according to the definitive diagnosis of pancreatic margin. Numbers in parentheses are the number of patients. HD, high-grade dysplasia; IC-IPMC, invasive cancer originating in intraductal papillary mucinous carcinoma; LD, low-grade dysplasia; MD, moderate dysplasia; MFT, median followup time; MI-IPMC, minimally invasive intraductal papillary mucinous carcinoma.

a statistically significant difference in the recurrence rates ($p < 0.001$). Overall survival curves are also provided, with 5-year survival rates of 100%, 82%, and 49% for noninvasive IPMC, MI-IPMC, and IC-IPMC, respectively ($p < 0.001$). Table 3 lists results of the univariate analysis for factors associated with recurrence. In the multivariate analysis, lymph node metastasis (+), serosal invasion (+), and carbohydrate antigen (CA)19-9 > 200 U/mL were significantly associated with recurrence among the significant predictive factors in the univariate analysis (Table 4).

DISCUSSION

IPMNs are frequently associated with flat (nonpapillary) extensions along the pancreatic ducts without cystic or duct-ectatic change, and preoperative imaging examinations often fail to detect such subtle findings, even if meticulous preoperative examinations, such as endoscopic ultrasonography or endoscopic retrograde pancreatography, are performed.[11-13,15] To secure a tumor-free margin, IOFSA during resection of IPMN is considered mandatory, and the reported incidence of positive first-time IOFSA is as high as 23% to 34%.[7-9,16]

In our series, 44 of 127 patients (35%) were positive for more than LD, and 18 (15%) were positive for more than HD at the initial IOFSA; 23% of the patients underwent additional resection. In the final IOFSA (ie, identical to the first IOFSA in patients who did not undergo additional resection), 106 (83%) were negative, 20 (16%) were positive for more than LD, and 1 (1%) was positive for cancer cells floating in the pancreatic duct (Table 1).

The clinical implications of positive pancreatic margins, especially with LD or MD (adenoma or borderline lesion), are controversial. The consensus guideline published in 2005 states that it is generally "believed" that adenomas and borderline lesions closer to adenoma do not warrant further resection, but borderline lesions with florid papillary formation may require further resection.[10] But no solid evidence to support this assumption is presented.

In this study, we analyzed the recurrence pattern after IPMN resection and showed that only 1 of 18 patients with pancreatic margins positive for LD or MD developed a recurrence, and the recurrence occurred in lymph nodes in a patient with IC-IPMC. Considering the low incidence and the extrapancreatic locus of the recurrence, a pancre-

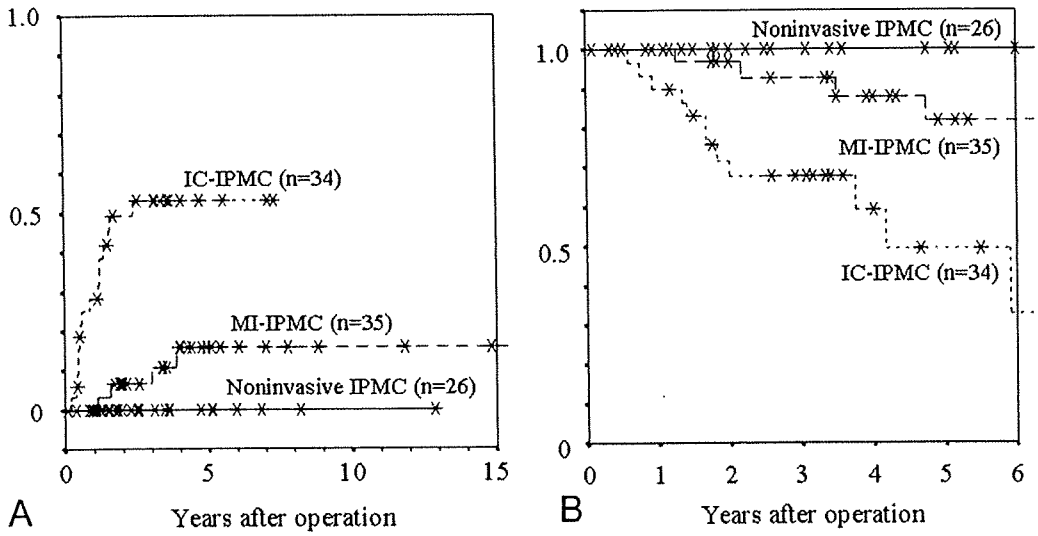

Figure 2. Comparison of (A) recurrence and (B) overall survival rates among patients with noninvasive intraductal papillary mucinous carcinoma (IPMC), minimally invasive IPMC (MI-IPMC), and invasive cancer originating in IPMC (IC-IPMC). There was a significant difference in recurrence and overall survival rates by the log-rank test ($p < 0.001$).

atic margin positive for LD or MD might not always warrant further resection, especially total pancreatectomy. On the contrary, among 20 patients who suffered from recurrence, all harbored invasive IPMCs (4 MI-IPMCs and 16 IC-IPMCs) in the resected specimen. Besides, in the multivariate analysis, the presence of lymph node metastasis, serosal invasion, and a high level of CA19-9 were the only significant factors associated with recurrence after IPMN resection (Table 4). These facts imply that recurrence after IPMN resection is determined primarily by the presence and stage of invasive IPMC rather than the status of the pancreatic margin. In this context, it might be more important for clinicians to detect and resect IPMCs at the preinvasive stage and, for patients with invasive IPMCs, to perform a radical pancreatic resection followed by systemic adjuvant chemotherapy, with the intention of preventing distant metastasis rather than merely performing additional pancreatic resections to achieve a negative margin.

In our series, IOFSA influenced operative procedures in 29 patients (23%) who underwent additional pancreatic resection and contributed to securing a tumor-free margin in a total of 105 patients (83%). But decision making according to IOFSA harbors two pitfalls that should be considered. First, accurate diagnosis is not always possible in a setting of IOFSA. In this study, 2 patients (2%) were misdiagnosed favorably in IOFSA compared with definitive diagnosis on hematoxylin and eosin. Couvelard and colleagues[7] also reported that a discrepancy between IOFSA and definite diagnosis exists in 6% of patients; Raut and associates[8] set the discrepancy rate at 13%. For accurate IOFSA, acquisition of a fresh and well-prepared specimen is important. In our institution, great care is given to preparing a frozen section that is as fresh as possible. For example, it is preferable to transect the pancreas by surgical scalpel rather than electric cautery, and the specimen is handled gently in order to avoid epithelial abrasion. In addition, diagnoses are made by attending pathologists who are familiar with IOFSA. The relatively high accuracy rate of IOFSA in this study may be attributed to the careful manipulation of a pancreatic stump, as well as to meticulous inspection by at least two pathologists specializing in pancreatic pathology.

Another problem is the multifocality of IPMN in the pancreas. Negative IOFSA does not always guarantee that there is no IPMN in the remnant pancreas. In other words, there is a possibility that another distinct IPMN resides or will arise in the remnant pancreas. But in this study, such multiple occurrences of IPMN were rare (only 2 patients), and both lesions were curatively resected during the routine followup period of 3 to 6 months. So we do not think that total pancreatectomy is needed very often if precise IOFSA and steady postoperative followup are provided.

In our institution, the management strategy of IPMN is as follows. All surgical candidates routinely undergo preoperative examinations of thin-sliced, contrast-enhanced multidetector row CT and extracorporeal ultrasonography. According to the calculated diagnostic scores, which were devised based on the investigation of predictive factors of malignancy among 123 resected cases of IPMN, we determine the operative indication of each IPMN patient, without using any invasive diagnostic procedures, such as

Table 3. Univariate Analysis of Factors Associated with Recurrence in Patients with Noninvasive and Minimally Invasive Intraductal Papillary Mucinous Carcinoma, and Patients with Invasive Cancer Originating in Intraductal Papillary Mucinous Carcinoma

Variable	n	Recurrence rate, % 1 y	3 y	5 y	p Value*
Gender					0.784
Male	55	5.7	23.5	28.6	
Female	40	15.3	23.7	23.7	
IPMN type					0.28
Branch type	28	11.1	15.2	15.2	
MPD/mixed type	67	9.4	26.9	30.0	
IC-IPMC in IPMN					< 0.001
(+)	34	28.4	53.2	53.2	
(−)	61	0	6.8	10.7	
Cancer in the initial IOFSA					0.025
(+)	18	29.4	47.0	47.0	
(−)	74	4.2	17.6	20.7	
IOFSA not done	3	33.3	33.3	33.3	
Cancer at the final pancreatic margin in the definitive diagnosis					0.755
(+)	3	33.3	33.3	33.3	
(−)	89	8.1	22.5	25.3	
IOFSA not done	3	33.3	33.3	33.3	
Cancer at surgical margin except for pancreatic cut margin					< 0.001
(+)	5	75.0	100	100	
(−)	90	6.8	19.5	22.2	
Lymph node metastasis					< 0.001
(+)	21	32.1	66.1	66.1	
(−)	74	4.1	11.2	14.5	
Serosal invasion					< 0.001
(+)	7	57.1	85.7	85.7	
(−)	88	5.9	17.7	20.5	
Retroperitoneal invasion					< 0.001
(+)	31	28.0	33.4	33.4	
(−)	64	1.6	8.2	12.3	
CEA (ng/mL)					0.327
≤ 5.0	71	7.5	19.4	19.4	
> 5.0	24	16.7	32.3	32.3	
CA19-9 (U/mL)					< 0.001
≤ 200	81	5.1	14.9	18.2	
> 200	14	35.7	64.3	64.3	

Serosal invasion refers to cancer cells invading the anterior capsule of the pancreas beyond the pancreatic parenchyma.
*Log-rank test.
CA 19-9, carbohydrate antigen 19-9; IC-IPMC, invasive cancer originating in IPMC; IOFSA, intraoperative frozen section analysis; IPMC, intraductal papillary mucinous carcinoma; MI-IPMC, minimally invasive IPMC; MPD, main pancreatic duct.

Table 4. Multivariate Analysis of Factors Associated with Recurrence in Patients with Noninvasive and Minimally Invasive Intraductal Papillary Mucinous Carcinoma and Patients with Invasive Cancer Originating in Intraductal Papillary Mucinous Carcinoma (n = 95)

Variable	p Value	Hazards ratio	95% CI
Serosal invasion	< 0.001	6.87	2.35–20.0
Lymph node metastasis	0.001	5.15	1.98–13.4
CA19-9 > 200 U/mL	0.023	3.00	1.17–7.73

CA19-9, carbohydrate antigen 19-9.

endoscopic ultrasound-guided cystic fluid cytology or pancreatic juice cytology by endoscopic retrograde pancreatography.[17] Operative procedures are planned based on meticulous assessment of preoperative multidetector row CT and ultrasonography, primarily focusing on the extent of ductal dilatation and spreading of papillary projections along the pancreatic ducts. Patients with suspected invasive cancer originating in IPMN (IC-IPMC) are immediately indicated for radical resection if there is no apparent distant metastasis or massive invasion of major vessels. Among patients without apparent invasive cancer, the malignant potential of each IPMN is classified according to the diagnostic scores, based on radiologic features. The size of the entire IPMN > 40 mm, presence of a mural nodule (> 3 mm) or thick septum (> 2 mm) inside the cystic lesion, and MPD or mixed type IPMNs are all features included in the scoring system. Operative indication is determined by balancing the malignant potential of IPMN with the risk of operation and life expectancy of the patient. If there are two simultaneous IPMN lesions that both fulfill the surgical indication, both lesions are resected at the same time. If there are multiple separated IPMNs, some fulfilling the surgical indication and others that do not, only the former are resected. In addition, the transection line of the pancreas is confirmed and finally determined by intraoperative ultrasonographic examination. The cut margin is usually at least more than 1 cm from the macroscopically detectable IPMNs.

Consequently, the positive IOFSA result in our series at best indicates the presence of a microscopically, but not macroscopically, detectable IPMN at the pancreas margin. The clinical implication of this might differ from that of a macroscopically detectable IPMN residing in the remnant pancreas. Considering that even a macroscopically detectable branch type intraductal papillary mucinous adenoma (IPMA) takes a few or more than 10 years until it evolves to invasive and life-threatening IPMC,[10,18] we do not think that these microscopic lesions with LD or MD (adenoma or borderline lesion) always deserve the additional resection, especially proceeding to a total pancreatectomy for an elderly patient. This idea is reinforced by the fact that re-

currence of IPMN in the remnant pancreas was rare in our analysis.

In this study, none of the 61 patients with noninvasive IPMN had a recurrence, regardless of the pancreatic margin status. In contrast, 20 of 69 patients (29%) with invasive IPMC developed a recurrence. Some investigators reported a similar low recurrence rate after resection of noninvasive IPMNs,[8,9] but others reported a relatively high recurrence rate (7.7% to 10%),[5,16,19] including a new occurrence of IPMN in the remnant pancreas, which was not common in our series. The cause of early recurrence might be partly from overlooking an invasive component in the resected specimens or in the remnant pancreas. We believe that recurrence in the remnant pancreas after resection of IPMN can be decreased by precise preoperative assessment of the entire pancreas, appropriate use of IOFSA, and complete resection of all IPMNs, fulfilling the operative indication as described in our resection strategy of IPMN.

The limitation of this study is that it is a retrospective study of more than 20 years, with a 41-month median followup; a much longer period might be necessary to accurately evaluate recurrence after IPMN resection, especially for benign lesions.

In conclusion, IOFSA contributed to secure a tumor-free margin in more than 80% of the patients who underwent IPMN resection. The positive margin with LD or MD does not always warrant further resection, especially a total pancreatectomy, considering the low recurrence rate in the remnant pancreas. Recurrence after IPMN resection is determined primarily by the presence and extent of the invasive cancer associated with IPMN.

Author Contributions

Study conception and design: Nara, Shimada
Acquisition of data: Nara, Esaki
Analysis and interpretation of data: Nara, Sakamoto, Kosuge, Hiraoka
Drafting of manuscript: Nara, Hiraoka
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