**Table 1.** Pathologic Diagnosis of Pancreatic Margin

| | Initial IOFSA | | Additional resection | | Final IOFSA* | | Definitive diagnosis on HE | |
|---|---|---|---|---|---|---|---|---|
| Diagnosis | 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

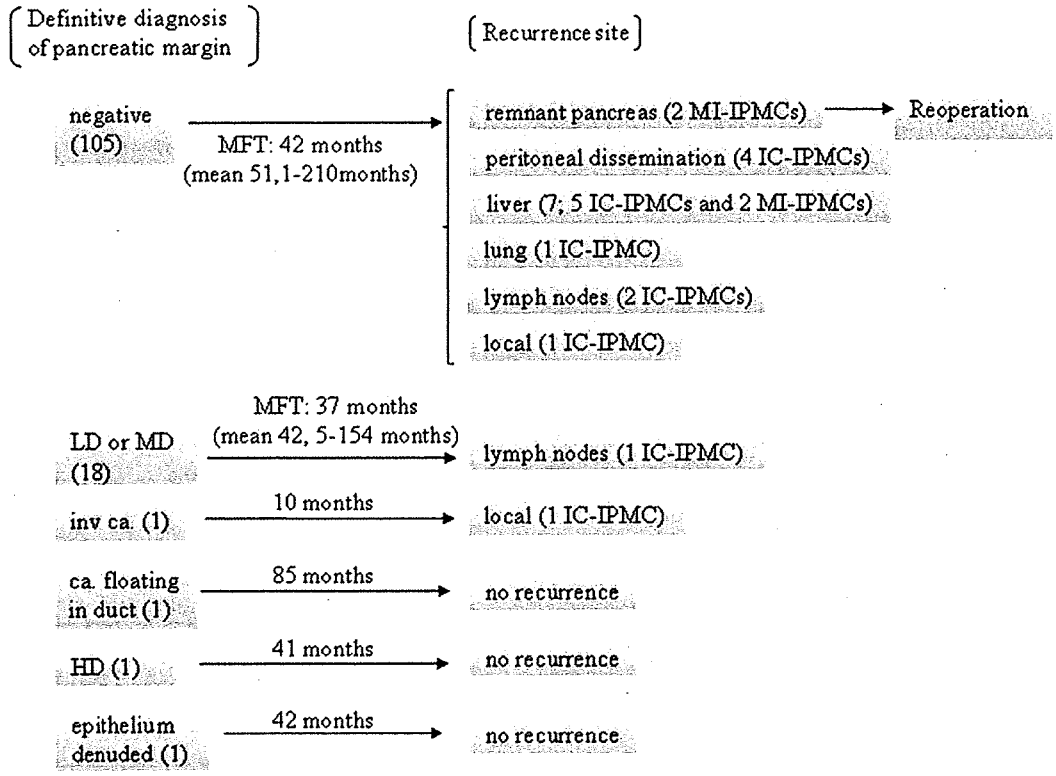


**Figure 1.** Recurrence sites after intraductal papillary mucinous neoplasm resection according to the definitive diagnosis of pancreatic margin. Numbers in parentheses are the number of patients. HD, high-grade dysplasia; IC-IPMC, invasive cancer originating in intraductal papillary mucinous carcinoma; 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-

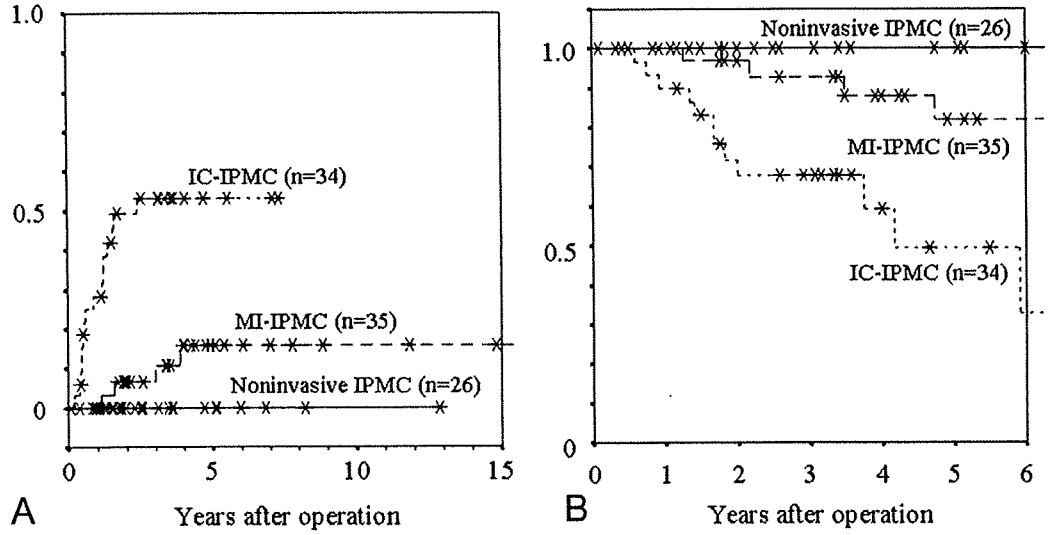


**Figure 2.** Comparison of (A) recurrence and (B) overall survival rates among patients with noninvasive intraductal papillary mucinous carcinoma (IPMC), minimally invasive IPMC (MI-IPMC), and invasive cancer originating in IPMC (IC-IPMC). There was a significant difference in recurrence and overall 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
Critical revision: Shimada, Sakamoto, Esaki, Kosuge

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# Preoperative Evaluation of Invasive and Noninvasive Intraductal Papillary-Mucinous Neoplasms of the Pancreas

## *Clinical, Radiological, and Pathological Analysis of 123 Cases*

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**Objective:** We aimed to investigate preoperative findings that are useful to distinguish intraductal papillary-mucinous neoplasm (IPMN) subtypes.

**Methods:** One hundred twenty-three patients who underwent pancreatectomy for IPMN were analyzed clinicopathologically and radiologically. Invasive IPM carcinomas (IPMCs) were subdivided into early-stage nonaggressive (minimally invasive IPMC [MI-IPMC]) and more advanced and aggressive (invasive carcinoma originating in IPMC [IC-IPMC]) subtypes according to our recently proposed pathological criteria.

**Results:** The lesions consisted of 27 IPMNs with low-grade dysplasia, 14 IPMNs with moderate dysplasia, 21 IPMNs with high-grade dysplasia, 30 MI-IPMCs, and 31 IC-IPMCs. Multidetector-row computed tomography detected a component of invasive carcinoma in IC-IPMC with 86% sensitivity and 100% specificity. In patients with IPMNs other than IC-IPMC, multivariate analysis demonstrated 3 significant predictive factors of malignancy: IPMN size (>40 mm), IPMN duct type (main pancreatic duct or mixed type), and the presence of a mural nodule or thick septum. The diagnostic score obtained using these 3 factors showed a strong correlation with the presence of malignancy.

**Conclusions:** For preoperative evaluation of patients with IPMN, it is recommended to rule out IC-IPMC using multidetector-row computed tomography and then to categorize IPMN other than IC-IPMC according to malignant potential based on the diagnostic score.

**Key Words:** intraductal papillary-mucinous neoplasm, pancreas, minimal invasion, diagnostic score, prognostic factor

(*Pancreas* 2009;38: 8–16)

Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas is a well-characterized entity both clinically and pathologically. IPMNs are characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae and lead to cystic dilation of the pancreatic ducts, forming a clinically and macroscopically detectable mass.[1,2] IPMNs include a wide spectrum of tumors that vary in their malignant potential. It is highly speculated that IPMN progresses from low-grade, moderate, and high-grade dysplasia (carcinoma in situ [CIS]) to invasive IPM carcinoma (IPMC) and eventually to invasive adenocarcinoma.[1–5] Depending on the grade of IPMN during the progression from noninvasive IPMN to invasive IPMC, the choice of treatment varies from a conservative approach to radical pancreatectomy with lymph node (LN) dissection.[6] Therefore, it is very important to determine the subtype of IPMN accurately before surgery to optimize the therapy.

Preoperative distinction of IPMN subtypes is not easy, even when multiple modalities are used.[7] It is necessary to inspect the entire lesion because various tumor grades are usually present in 1 lesion; however, this is problematic to perform directly and biopsy of the lesion is difficult because IPMNs are located in the pancreas and often shows cystic features. Some groups reported the high accuracy of pancreas juice cytology[8] or peroral intraductal pancreatoscopy,[9] but these procedures require expertise and are not free from complications; thus, routine practice of these modalities remains limited.

Previous studies have proposed some factors that are predictive of IPMN malignancy, such as the presence of symptoms (particularly jaundice), positive pancreatic juice cytology, tumor size greater than 30 to 50 mm, main pancreatic duct (MPD) type or mixed type, dilatation of MPD, the presence of a mural nodule, papillary projection, a thick septum, and wall thickening.[7,8,10–12] Except for the former two, these features can be observed by radiological examination, but these factors are not always related to the malignancy, and none of them can be used alone.

Another problem is that no unequivocal pathological criteria for distinguishing invasive IPMC have been established. The recent consensus is that the malignant potential of IPMN is dependent on the presence of invasive cancer and its extent.[13–19] However, invasive IPMC categorized by the Armed Forces Institute of Pathology (AFIP) and World Health Organization classifications[1,2] covers cancer with variable biological behavior, with the 5-year survival rate varying substantially between 24% and 60%.[13–19] Therefore, invasive IPMC should be regarded separately as either aggressive or nonaggressive. The classification of the Japan Pancreas Society subdivides invasive IPMC into minimally invasive IPMC (MI-IPMC) and invasive carcinoma originating in IPMC (IC-IPMC) (Fig. 1).[20] Minimally invasive IPMC represents invasive IPMC with early-stage nonaggressive characteristics, whereas IC-IPMC represents a more advanced tumor. Minimally invasive IPMC has been reported to have a better surgical outcome than IC-IPMC,[21,22] although the criteria used for defining MI-IPMC are still unclear.[20] Recently, we

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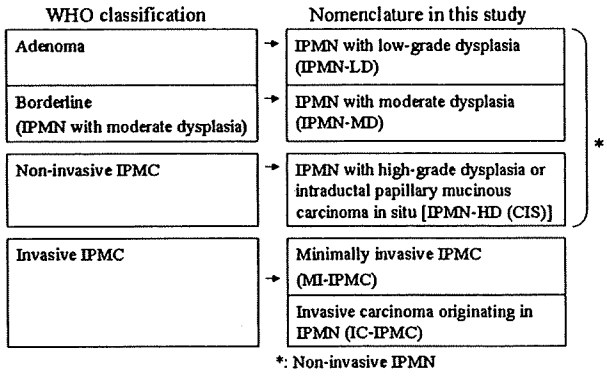


**FIGURE 1.** The nomenclature of IPMN used in this study is based on AFIP classification[1] and corresponded to the World Health Organization classification.[2] Invasive IPMCs are further divided into MI-IPMC and IC-IPMC according to our diagnostic criteria,[23] which is based on the classification of the Japan Pancreas Society.[20]

proposed simple and practical diagnostic criteria for MI-IPMC[23] and used them to classify IPMN in 104 patients. Those with MI-IPMC showed a good outcome similar to that of noninvasive IPMN after curative resection, whereas patients with IC-IPMC showed a worse outcome similar to that of conventional ductal carcinoma of the pancreas. In addition, IC-IPMCs were frequently associated with LN metastasis, necessitating LN dissection during operation, whereas no LN metastasis was observed among patients with MI-IPMCs.[22,23] Thus, precise discrimination between MI-IPMC and IC-IPMC is important not only for predicting the postoperative outcome, but also for deciding the operative procedure.

In the present retrospective study, we examined 123 patients with IPMN and assessed their clinical and radiological findings for preoperative prediction of IPMN pathological subtypes.

## MATERIALS AND METHODS

### Study Population

This study was approved by the ethics committee of the National Cancer Center, Japan. Between January 1984 and December 2006, a total of 123 patients underwent pancreatectomy for IPMN at the National Cancer Center Hospital, Japan. Seventy-eight (63%) of the surgical operations were performed after January 2001. Eight patients who also had ductal carcinoma of the pancreas that was not directly associated with IPMN were excluded from the study. The study patients are composed of 70 men and 53 women aged 40 to 84 years (mean, 64.7 years). Upon pathological examination, 5 patients were found to have multiple IPMNs in the resected specimen. We chose 1 lesion with the highest grade, then the largest lesion among multiple IPMNs, and used it for this study. Clinical data and characteristics of the IPMNs are summarized in Table 1. Every patient was followed up in the outpatient clinic every 1 to 3 months during the first postoperative year, and every 6 to 12 months thereafter. No patient was lost to follow-up. Clinical and laboratory data for every patient were obtained from the medical records.

### Pathological Examination

All of the IPMNs were pathologically reexamined, and the diagnosis of IPMN was confirmed. Surgically resected specimens were fixed in 10% formalin and cut into serial 5-mm-thick slices, horizontally in the pancreas head and sagittally in the

**TABLE 1.** Demography of Patients With IPMNs

| Pathological Diagnosis | IPMN-LD or IPMN-MD (n = 41) | IPMN-HD (CIS) (n = 21) | MI-IPMC (n = 30) | IC-IPMC (n = 31) | Total (n = 123) | *P* |
|---|---|---|---|---|---|---|
| Mean age, yrs | 64.1 ± 8.0 | 62.0 ± 9.6 | 64.9 ± 8.6 | 67.4 ± 10.4 | 64.7 ± 9.1 | 0.186 |
| Median age (range), yrs | 65 (42–77) | 60 (40–80) | 66 (41–76) | 69 (45–84) | 66 (40–84) | |
| Male, % | 25 (61.0%) | 10 (47.6%) | 19 (63.3%) | 16 (51.6%) | 70 (56.9%) | 0.599 |
| Chief complaints | | | | | | 0.024* |
| Complaints (−) | 27 | 13 | 15 | 12 | 67 | |
| Complaints (+) | 14 | 8 | 15 | 19 | 56 | |
| Radiological findings | | | | | | |
| Tumor location | | | | | | 0.005 |
| Ph included | 29 | 15 | 22 | 12 | 78 | |
| Ph excluded | 12 | 6 | 8 | 15 | 41 | |
| Total pancreas (diffuse) | 0 | 0 | 0 | 4 | 4 | |
| rIPMN size, mm | 35.7 ± 16.2 | 44.5 ± 17.4 | 53.6 ± 31.6 | 48.4 ± 30.1 | 44.8 ± 25.4 (10–136) | 0.022 |
| rMPD diameter, mm | 4.5 ± 2.8 | 6.5 ± 4.8 | 10.7 ± 6.6 | 6.4 ± 4.5 | 6.9 ± 5.2 (1–31) | <0.001 |
| rIPMN type | | | | | | <0.001 |
| rMPD type | 0 | 5 | 11 | 10 | 26 | |
| rBD type | 33 | 12 | 6 | 8 | 59 | |
| rMixed type | 8 | 4 | 13 | 13 | 38 | |
| Mural nodule (>3 mm), % | 10 (24%) | 15 (71%) | 20 (67%) | 15 (48%) | 60 (49%) | <0.001 |
| Thick septum (>2 mm), % | 11 (27%) | 8 (38%) | 14 (47%) | 13 (42%) | 46 (37%) | 0.343 |
| Size of invasive cancer, mm | — | — | <5 | 36.1 ± 17.7 (6–90) | — | |

*Comparison between noninvasive IPMN and invasive IPMN (MI-IPMC + IC-IPMC) by $\chi^2$ test.

Ph indicates pancreas head; rIPMN size, IPMN size measured on CT; rIPMN type, IPMN type determined based on CT findings.

pancreas body and tail. All the sections were stained with hematoxylin and eosin for pathological examination. After histopathological examination of all the sections, the lesion was classified as IPMN with low-grade dysplasia (IPMN-LD), moderate dysplasia (IPMN-MD), high-grade dysplasia (IPMN-HD; CIS), or invasive IPMC according to the AFIP classification.[1] The lesion was graded by the highest degree of atypia. Invasive IPMCs were further divided into MI-IPMC or IC-IPMC according to our proposed criteria.[23] We classified the invasive features of IPMC into 3 patterns: infiltrative growth, mucous rupture, and expansive growth. *Infiltrative growth* is an invasive pattern commonly seen in conventional ductal carcinoma of the pancreas, showing tubular or mucinous invasion. On the other hand, mucous rupture and expansive growth are unique features of IPMC, which grows expansively with large amounts of mucus secretion. *Mucous rupture* refers to mucous lakes around an intraductal IPMC, sometimes containing scanty floating cancer cells, formed by rupture of pancreatic ducts through intraductal high pressure. *Expansive growth* refers to the loss of the basement membrane because of marked dilatation of pancreatic duct, sometimes resulting in the involvement (erosion or fistula formation) of the bowel wall or major vessels. We defined *minimal invasion* as (*a*) an infiltrative growth of 5 mm or less, (*b*) mucous rupture not associated with infiltrative growth of more than 5 mm, or (*c*) expansive growth without fistula formation with major vessels. And when at least 1 feature beyond the previously mentioned criteria of minimal invasion was present, the lesion was diagnosed as IC-IPMC. Invasive carcinoma originating in IPMC was originally defined as a lesion consisting of IPMN and invasive carcinoma with predominance of the IPMN component.[20] This type of invasive carcinoma shows continuous transition between invasive carcinoma and intraductal IPMC. In this study, we also included a new group in which invasive carcinoma apparently originated from IPMN but was predominant over the IPMN component because there was no statistically significant survival difference between IC-IPMCs with predominant IPMN component and IC-IPMCs with predominant invasive cancer component in our preliminary analysis.

The measured size of an IPMN (excluding the invasive component) was denoted as the *pIPMN size*, defined as the maximum diameter of microscopically recognized noninvasive IPMN. The size of invasive cancer was measured separately in patients with MI-IPMC and IC-IPMC. The duct type of IPMN was also determined according to where the IPMN was mainly present. When the IPMN was located mainly in the MPD and extended to a small region of the branch duct (BD) (length, <1 cm), it was defined as the MPD type. When the IPMN located mainly in the BD and extended to a small region of the

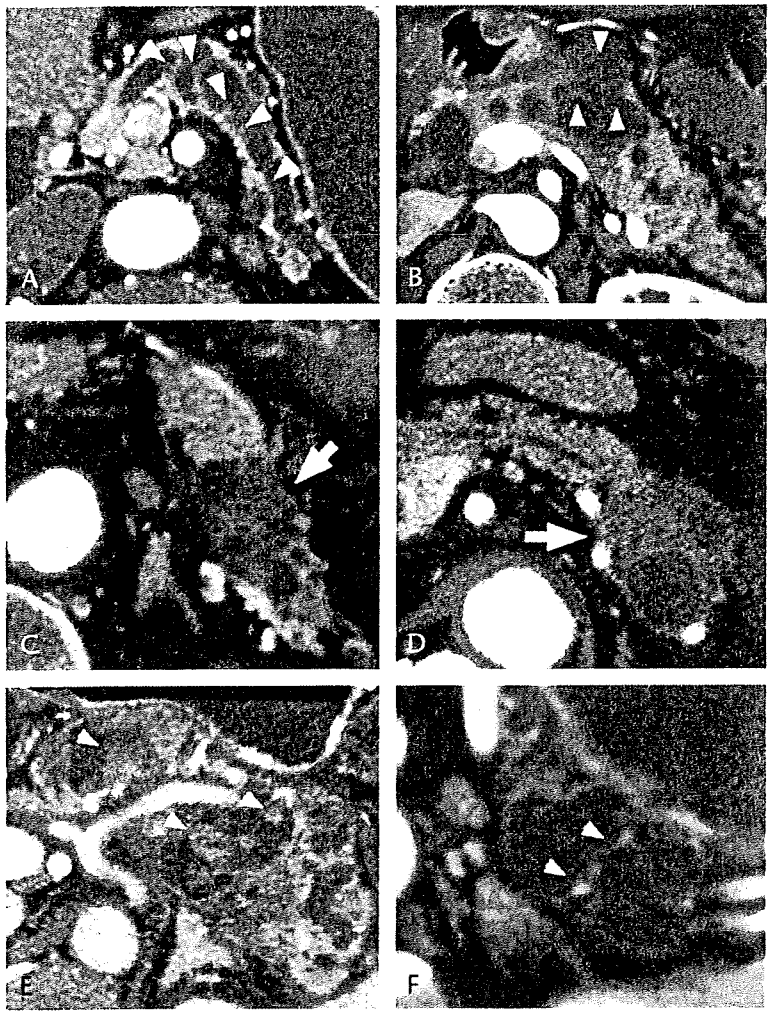


**FIGURE 2.** A and B, MDCT images show papillary projections in the dilated pancreatic ducts (arrowheads). Papillary projections appear as subtle brushlike low attenuations along the wall of the pancreatic ducts, reflecting the extent of IPMN. C and D, MDCT images of IC-IPMCs. The invasive cancer components (arrows) are depicted as areas of low attenuation adjacent to or surrounding the cystic IPMN lesions. The retropancreatic invasion adjacent to the splenic artery is shown (arrow) (D). E and F, MDCT images showing mural nodules (E) and thick septa (F). E, Various-sized mural nodules are evident in the intraductal carcinoma component (arrowheads). F, The thick septum is indicated by arrowheads in noninvasive IPMCs.

MPD (length, <1 cm), it was defined as the BD type; otherwise, the IPMN was defined as the mixed type.

## Radiological Examination

All 123 patients underwent contrast-enhanced computed tomography (CT) and extracorporeal ultrasonography (US) examinations, whereas magnetic resonance cholangiopancreatography (MRCP) was performed in 77 patients (63%). As endoscopic retrograde cholangiopancreatography and endoscopic US are not routinely performed at our institution, data for both examinations were excluded from the present analysis. The CT images were obtained using single-slice helical CT machines before 2000, and thereafter using multidetector-row CT (MDCT) with a 1- to 2-mm section thickness. Of the 123 patients, 71 (58%) underwent MDCT examinations.

The CT images were retrospectively reviewed independently by 2 investigators (S.N. and H.O.) without knowledge of the pathological diagnosis. Discrepancy was less than 5%, and cases with disagreement were resolved by discussion. The size of the IPMN (designated as rIPMN size), the duct type

TABLE 2. Univariate Analysis of Preoperative (Clinical or Radiological) Findings Associated With Subtypes of IPMNs

| Variables | (1) IPMN-LD or IPMN-MD (n = 41) | (2) IPMN-HD (CIS) (n = 21) | (3) MI-IPMC (n = 30) | (4) IC-IPMC (n = 31) | Total (n = 123) | $P$ ($\chi^2$ or Fisher Exact Test) (2) (3) vs (4) | (1) vs (2) (3) | (2) vs (3) |
|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | 0.643 | 0.690 | 0.265 |
| Male | 25 | 10 | 19 | 16 | 70 | | | |
| Female | 16 | 11 | 11 | 15 | 53 | | | |
| Age, yrs | | | | | | 0.020 | 0.858 | 0.969 |
| ≤70 | 32 | 16 | 23 | 16 | 87 | | | |
| >70 | 9 | 5 | 7 | 15 | 36 | | | |
| Chief complaint | | | | | | 0.155 | 0.287 | 0.400 |
| (−) | 27 | 13 | 15 | 12 | 67 | | | |
| (+) | 14 | 8 | 15 | 19 | 56 | | | |
| Jaundice | | | | | | 0.098 | 0.500 | 0.506 |
| (−) | 41 | 21 | 28 | 26 | 116 | | | |
| (+) | 0 | 0 | 2 | 5 | 7 | | | |
| CEA, ng/mL | | | | | | 0.288 | 0.376 | 0.134 |
| ≤10 | 40 | 21 | 26 | 26 | 113 | | | |
| >10 | 1 | 0 | 4 | 5 | 10 | | | |
| CA-19-9, U/mL | | | | | | <0.001 | 0.296 | 0.119 |
| ≤37 | 31 | 20 | 23 | 10 | 84 | | | |
| >37 | 10 | 1 | 7 | 21 | 39 | | | |
| Radiological findings | | | | | | | | |
| Detection of invasive cancer on CT* | | | | | | <0.001 | 0.126 | 0.134 |
| (−) | 41 | 21 | 26 | 6 | 94 | | | |
| (+) | 0 | 0 | 4 | 25 | 29 | | | |
| Tumor location | | | | | | 0.055 | 0.847 | 0.881 |
| Ph included | 29 | 15 | 22 | 16 | 82 | | | |
| Ph excluded | 12 | 6 | 8 | 15 | 41 | | | |
| Tumor distribution | | | | | | 0.110 | 0.532 | 0.034 |
| 1 segment | 35 | 20 | 21 | 20 | 96 | | | |
| 2 or 3 segments | 6 | 1 | 9 | 11 | 27 | | | |
| rIPMN size, mm | | | | | | 0.321 | <0.001 | 0.917 |
| ≤40 | 31 | 8 | 11 | 15 | 65 | | | |
| >40 | 10 | 13 | 19 | 16 | 58 | | | |
| rMPD diameter, mm | | | | | | 0.120 | 0.005 | 0.020 |
| ≤8 | 36 | 17 | 14 | 24 | 91 | | | |
| >8 | 5 | 4 | 16 | 7 | 32 | | | |
| rIPMN duct type | | | | | | 0.371 | <0.001 | 0.006 |
| rMPD or rMixed | 8 | 9 | 24 | 23 | 64 | | | |
| rBD | 33 | 12 | 6 | 8 | 59 | | | |
| Mural nodule (>3 mm) or thick septum (>2 mm) | | | | | | 0.079 | 0.001 | 0.969 |
| (−) | 24 | 5 | 7 | 13 | 49 | | | |
| (+) | 17 | 16 | 23 | 18 | 74 | | | |

*CT images obtained using both single-slice helical CT and MDCT.
CEA indicates carcinoembryonic antigen; Ph, pancreas head.

of IPMN (designated as rIPMN duct type, and MPD, BD, and mixed type being denoted as rMPD, rBD, and rMixed type, respectively), the distribution of IPMN (head/uncus, body, or tail), and the MPD diameter (designated as rMPD diameter) were determined. The *rIPMN size* was defined as the maximum diameter of an entire noninvasive IPMN lesion, including not only the definitely cystic and/or intraductal papillary component, but also subtle papillary projections reflecting spread along the pancreatic duct (Figs. 2A, B).[24] The invasive component was excluded from the measurement of rIPMN size. The size of invasive component was measured separately depending on the CT findings. The presence of invasive carcinoma in patients with IC-IPMC was regarded as positive when an irregularly shaped hypoattenuating solid mass was detected adjacent to or surrounding an IPMN on contrast-enhanced CT.[25] The replacement of the pancreatic parenchyma by a hypoattenuating solid mass, proliferation into the extrapancreatic tissue, and encasement of surrounding vessels were all regarded as signs of invasion, similarly to the conventional invasive ductal carcinoma of the pancreas (Figs. 2C, D). We also assessed the presence of a mural nodule (if its size was >3 mm; Fig. 2E)[10] or a thick septum (if its size was >2 mm; Fig. 2F)[12] on image analysis including CT, US, and MRCP, if available.

## Statistical Analysis

Continuous data were presented as mean ± SD. The cutoff values for rIPMN and pIPMN size for differentiating benign and malignant lesions were investigated by constructing receiver operating characteristic (ROC) curves. Differences between categorical variables were evaluated using $\chi^2$ test or Fisher exact test. One-way analysis of variance was used to compare the means of 3 or more groups. Significant predictors in the univariate analysis were included in a backward stepwise logistic regression model for multivariate analysis. Differences at $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 11.0J software (SPSS Inc, Chicago, Ill).

# RESULTS

Postoperative pathological examination revealed that the studied lesions are composed of 27 IPMN-LDs, 14 IPMN-MDs, 21 IPMN-HD (CIS), 30 MI-IPMCs, and 31 IC-IPMCs (Table 1). More than half of the IPMNs were discovered incidentally in asymptomatic patients during health check-up or follow-up examinations after treatment of other organ diseases, and such cases were significantly common among noninvasive IPMNs ($P = 0.024$; Table 1). Chief complaints at the initial presentation included abdominal pain (n = 28), exacerbation of diabetes mellitus (n = 9), back pain (n = 7), jaundice (n = 7), weight loss (n = 7), appetite loss (n = 4), general fatigue (n = 2), carbohydrate antigen 19-9 (CA-19-9) elevation (n = 2), vomiting (n = 1), and fever (n = 1).

TABLE 3. Multivariate Analysis of Preoperative (Clinical or Radiological) Findings Associated With Subtypes of IPMNs

| | Odds Ratio (95% CI) | P* |
|---|---|---|
| IPMN-HD (CIS) and MI-IPMC vs IC-IPMC | | |
| Invasive cancer detected on CT† | 53.9 (14.0–208) | <0.001 |
| CA-19-9 >37 U/mL | 4.38 (1.22–15.8) | 0.0024 |
| IPMN-LD or IPMN-MD vs IPMN-HD (CIS) and MI-IPMC | | |
| rMPD or rMixed type | 4.92 (1.75–13.8) | 0.003 |
| Mural nodule or thick septum (+) | 2.97 (1.08–8.14) | 0.035 |
| rIPMN size >40 mm | 2.88 (1.04–8.02) | 0.042 |
| IPMN-HD (CIS) vs MI-IPMC | | |
| rMPD or rMixed type | 5.33 (1.54–18.5) | 0.008 |

*Logistic regression analysis (backward stepwise method).
†CT images obtained using both single-slice helical CT and MDCT.

TABLE 4. Accuracy of CT Detection of Invasive Cancer in IC-IPMC

**A. MDCT**

| Pathological diagnosis | CT detection of invasive cancer (+) | (−) | Sensitivity 86% Specificity 100% |
|---|---|---|---|
| IC-IPMC (+) | 18 | 3 | 21 |
| IC-IPMC (−) | 0 | 50 | 50 |
| | 18 | 53 | 71 |

**B. Single-slice helical CT**

| Pathological diagnosis | CT detection of invasive cancer (+) | (−) | Sensitivity 70% Specificity 90% |
|---|---|---|---|
| IC-IPMC (+) | 7 | 3 | 10 |
| IC-IPMC (−) | 4 | 38 | 42 |
| | 11 | 41 | 52 |

## Preoperative Detection of IC-IPMC

To test which preoperative (clinical and radiological) variables were closely associated with IPMN pathological subtypes, their relationship was examined (Table 2). As reported previously,[21–23,26] the postoperative outcome of patients with IC-IPMC was significantly worse than that of patients with MI-IPMC or noninvasive IPMN, and LN metastasis was exclusively associated with IC-IPMC, underlining the importance of preoperative detection of IC-IPMC for therapeutic planning. Univariate analysis showed that the following preoperative variables were closely associated with the pathological subtypes of IC-IPMC: older than 70 years, the presence of invasive cancer detected on CT (both single-slice helical CT and MDCT), and CA-19-9 greater than 37 U/mL (Table 2). Multivariate analysis showed

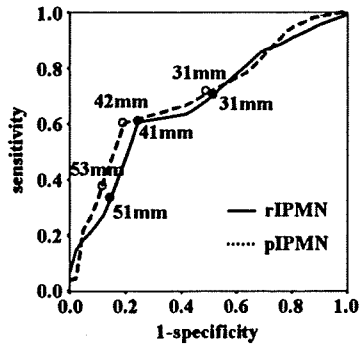


FIGURE 3. The ROC curves of rIPMN and pIPMN size. The optimal cutoff values of rIPMN and pIPMN size for detection of malignancy (carcinoma positive in a lesion) were 41 and 42 mm, respectively.

that the presence of invasive cancer detected on CT (both single-slice helical CT and MDCT) and CA-19-9 greater than 37 U/mL were significant predictive variables for IC-IPMC (Table 3).

We then analyzed how precisely CT was able to detect invasive cancers in patients with IC-IPMC. Among the 71 patients who underwent MDCT, the presence of IC-IPMC was detected with 86% sensitivity and 100% specificity, whereas single-slice helical CT (n = 52) showed 70% sensitivity and 90% specificity. Thus, the overall sensitivity and specificity of CT (n = 123) to detect invasive cancer in patients with IC-IPMC were 81% and 96%, respectively (Table 4).

## Preoperative Evaluation of IPMNs Other Than IC-IPMC

We investigated the clinical and radiological findings correlated with subtypes of IPMN other than IC-IPMC (n = 92; Table 2). We excluded IC-IPMCs in which invasive cancer was not detected by CT because we aimed to clarify the characteristics of pathologically proven IPMN-HD (CIS) and MI-IPMC. Our previous study showed no significant difference in the postoperative outcome between patients with noninvasive IPMN and MI-IPMC, although 2 of 26 patients with MI-IPMC experienced recurrence.[23] Other groups also reported that 2 of 17 patients with noninvasive IPMC (IPMN-HD [CIS]) had recurrent invasive carcinoma,[13] and that 1 of 14 patients with noninvasive IPMC (IPMN-HD [CIS]) and 1 of 6 patients with MI-IPMC had recurrence after surgery.[22] Thus, preoperative detection of IPMN-HD (CIS) and MI-IPMC is a clinically important consideration, as much as the detection of IC-IPMC. The optimal cutoff values of rIPMN and pIPMN size for the detection of malignancy (IPMN-HD [CIS] and MI-IPMC) were determined to be 41 and 42 mm, respectively, on the basis of the ROC curve (Fig. 3); therefore, we adopted a cutoff value of 40 mm for rIPMN size. Univariate analysis showed that the following variables were significantly associated with malignant IPMC other than IC-IPMC: rIPMN size greater than 40 mm, rMPD diameter greater than 8 mm, rMPD or rMixed type, and the presence of a mural nodule or thick septum (Table 2). Multivariate analysis showed that rIPMN size greater than 40 mm, rMPD or rMixed type, and the presence of a mural nodule or thick septum were significant predictive factors of malignancy (Table 3).

TABLE 5. Diagnostic Score and Results in Patients With IPMN Other Than IC-IPMC (n = 92)

**A. Diagnostic score (the sum of acquired points)**

| Predictive variables | Acquired point |
|---|---|
| rMPD or rMixed type | Yes, 1; No, 0 |
| Presence of mural nodule or thick septum | Yes, 1; No, 0 |
| rIPMN size >40 mm | Yes, 1; No, 0 |

**B. Comparison of diagnostic score between patients with benign IPMN (IPMN-LD and IPMN-MD) and patients with malignant IPMN (IPMN-HD [CIS] and MI-IPMC)**

| Score | Benign | Malignant | Total | Risk ratio of presence of carcinoma | 95% CI |
|---|---|---|---|---|---|
| 0 | 18 (86%) | 3 (14%) | 21 | 0.13 | 0.042–0.42 |
| 1 | 14 (56%) | 11 (44%) | 25 | 0.63 | 0.32–1.2 |
| 2 | 6 (25%) | 18 (75%) | 24 | 2.4 | 1.1–1.5 |
| 3 | 3 (14%) | 19 (86%) | 22 | 5.1 | 1.6–16.0 |

**C. Comparison of diagnostic score between patients with noninvasive IPMN (IPMN-LD, IPMN-MD, and IPMN-HD [CIS]) and patients with MI-IPMC**

| Score | Noninvasive IPMN | MI-IPMC | Total | Risk ratio of presence of carcinoma | 95% CI |
|---|---|---|---|---|---|
| 0 | 20 (95%) | 1 (5%) | 21 | 0.10 | 0.015–0.73 |
| 1 | 19 (76%) | 6 (24%) | 25 | 0.65 | 0.29–1.5 |
| 2 | 15 (63%) | 9 (38%) | 24 | 1.2 | 0.61–2.5 |
| 3 | 8 (36%) | 14 (64%) | 22 | 3.6 | 1.7–7.7 |

Numbers in parentheses denote the percentage of the number in the *Total* column.

## Effectiveness of Diagnostic Score for Prediction of Noninvasive IPMC and MI-IPMC

It was unlikely that any of these preoperative variables (Table 3) alone would facilitate the accurate prediction of IPMN pathological subtypes (Table 2); therefore, we tried to predict the pathological subtypes of IPMN accurately by combining 3 variables: rIPMN size, rIPMN duct type, and the presence of a mural nodule or thick septum. A diagnostic score was devised with the aim of preoperatively identifying patients at high risk for malignancy among patients with IPMN other than IC-IPMC. The score was calculated by assigning 1 point for each of rIPMN size greater than 40 mm, rMPD or rMixed type, and mural nodule or thick septum detected on preoperative images (Table 5). The rates of malignancy (ie, IPMN-HD [CIS] and MI-IPMC) were 14%, 44%, 75%, and 86% in the patient groups with diagnostic scores of 0, 1, 2, and 3, respectively. The risk ratio of carcinoma among patients with a score 2 or 3 was 3.3 (95% confidence interval [CI], 1.8–6.0).

Comparison between IPMN-HD (CIS) and MI-IPMC showed that tumor distribution in 2 or 3 segments, MPD diameter greater than 8 mm, and rMPD or rMixed type were significantly associated with MI-IPMC by univariate analysis (Table 2), and rMPD or rMixed type remained significant by multivariate analysis (Table 3). The rates of minimal invasion were 5%, 24%, 38%, and 64% in the patient groups with diagnostic scores of 0, 1, 2, and 3, respectively (Table 5). The risk ratio of minimal invasion among patients with a score of 3 was 3.6 (95% CI, 1.7–7.7).

## DISCUSSION

Recent studies on the natural history of IPMNs have revealed that the prevalence of malignancy is substantially low in small (<3 cm) BD-type IPMNs without mural nodules[27] and that it takes a relatively long period until noninvasive IPMNs progress to invasive IPMCs.[28] In addition, the current consensus regarding the malignant potential of IPMN is that its aggressiveness is dependent on the presence of invasive cancer, the extent of cancer invasion, and the biological characteristics of cancer cells.[13–19] Furthermore, MI-IPMC shows nonaggressive characteristics similar to noninvasive IPMN, whereas IC-IPMC has aggressive characteristics comparable to conventional ductal carcinoma of the pancreas.[23] These findings suggest that the therapeutic strategy for IPMN ought to differ according to the grade. Conservative treatment may be possible in selected cases of early-stage noninvasive IPMN.[29] Function-preserving pancreatectomy may be a treatment option in some noninvasive IPMNs.[30] On the other hand, as IC-IPMCs are often associated with LN metastasis[22,23] (an incidence of 61% at our institution), radical pancreatectomy with LN dissection is necessary for curative resection. Therefore, it is becoming more important to

categorize IPMN preoperatively into its corresponding pathological subtypes accurately.

Here, we retrospectively studied 123 patients who underwent surgical resection of IPMN and analyzed which preoperative findings could precisely predict the pathological subtypes. We found that MDCT was able to detect the presence of invasive cancer in IC-IPMC with 86% sensitivity and 100% specificity. We also found that rIPMN size greater than 40 mm, rMPD or rMixed type, and the presence of a mural nodule or thick septum were significant predictive factors of malignancy by multivariate analysis in patients with IPMNs other than IC-IPMC. Furthermore, the diagnostic score obtained using these 3 predictive factors showed a good correlation with the presence of carcinoma.

The clinical and radiological features of IC-IPMC are substantially different from other IPMNs. The IC-IPMCs are frequently associated with high levels of serum CA-19-9, and the invasive component of IC-IPMCs is frequently visible on CT (Table 3). These features of IC-IPMC, combined with the poor postoperative prognosis and high rate of LN metastasis, indicate that we should separate IC-IPMC from other IPMNs and treat them similarly to conventional invasive ductal carcinoma of the pancreas. When IC-IPMC is present, aggressive treatment ordinarily applied to the conventional pancreatic cancer may be indicated. This is in marked contrast with the fact that LN metastasis is almost zero in noninvasive IPMC or MI-IPMCs, and function-preserving surgery could be indicated for this patient group. Thus, we think clinicians should pay more attention to detect an associated invasive carcinoma (IC-IPMC) at initial diagnosis of IPMN.

On the basis of these findings, we propose a 2-step algorithm for determining the therapeutic strategy for patients with IPMN (Fig. 4). For the first step, patients with IPMN are categorized according to whether MDCT reveals an invasive cancer (IC-IPMC) in the lesion. For the second step, patients with IPMN other than IC-IPMC are categorized according to whether the diagnostic score suggests the presence of malignancy (Table 5). The malignancy rate was significantly high (risk ratio, 3.3; $P < 0.001$) in patients with a diagnostic score of 2 or 3. Malignancy in IPMN was detected in patients with a diagnostic score of 2 or 3, with 73% sensitivity and 78% specificity; thus, these patients should be taken to an immediate surgical operation to resect the IPMN. For patients with a diagnostic score of 1, resection is advocated for low-risk patients with a reasonable life expectancy, considering that about half (44%) of this patient group had carcinoma, although the relative risk of malignancy is lower than in patients with a diagnostic score of 2 or 3. Patients with a diagnostic score of 0 had the lowest risk of malignancy (0.13 [95% CI, 0.042–0.42]). In our series, the diagnostic score of 0 indicated IPMN as a benign lesion with 44% sensitivity and 94% specificity. Combined with previous reports showing a low occurrence rate of invasive cancer in this patient group,[28,29] these findings suggest that careful nonoperative management may be applicable for selected patients, especially those who are older or have severe complications; however, it should not be ignored that 3 (14%) of 21 patients in this group harbored carcinoma (Table 5B). Thus, "wait-and-watch" management is not always recommended for patients with a diagnostic sore of 0, and conservative treatment may be applicable in selected cases with well-informed consent about the risk of malignancy. Further accumulation of patients' follow-up data on the natural history of IPMN or the emergence of new accurate molecular markers is necessary to establish more relevant criteria for the observation strategy. Currently, balancing the malignant potential of IPMN with the risk of surgery and life expectancy may be the most practical approach for determining the indication and extent of surgery.

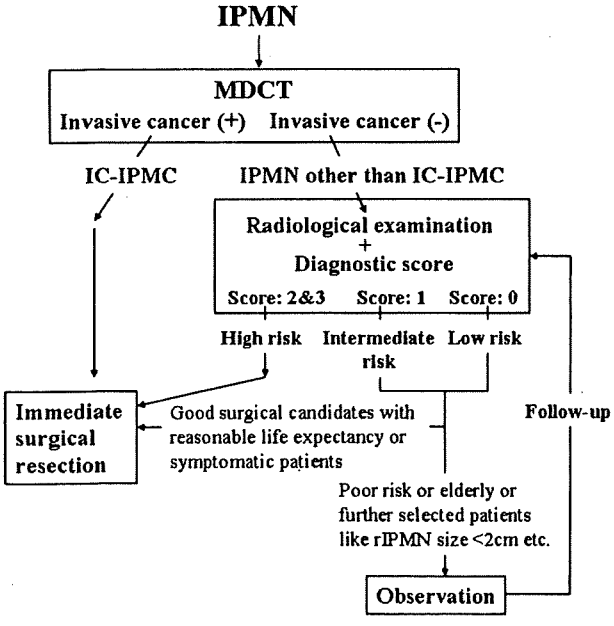


FIGURE 4. Proposed treatment algorithm for preoperative evaluation of patients with IPMN.

In this study, we were able to detect a component of invasive carcinoma in IC-IPMC using MDCT, with 86% sensitivity and 100% specificity, regardless of the size of invasive cancer. This is compatible with a recent report from another group, in which MDCT detected invasive IPMN with high sensitivity and specificity.[25] Although some authors have emphasized the diagnostic advantage of MRCP for the detection of cystic lesions,[31,32] its ability to detect solid invasive cancer associated with IPMN has not been well established. Other authors have reported that MDCT has marked ability to detect small conventional invasive cancers of the pancreas.[33,34] Although we have not yet compared the abilities of MDCT with those of MRCP for the detection of IC-IPMC, the present study has provided evidence that MDCT is very useful for the accurate detection of IC-IPMC. In our series, MDCT produced no false-positive images of patients with IC-IPMC, although it is possible that inflammatory change in the adjacent pancreatic parenchyma may be misdiagnosed as invasive cancer, as has been reported in cases of conventional invasive cancer of the pancreas.[35] Furthermore, the invasion of mucinous carcinoma may be misinterpreted as an ordinary cystic lesion without invasion.

Pathological examination revealed that IPMNs formed cystic or macroscopically papillary lesions and often spread to the surrounding pancreatic ducts. Low papillary features or spreading to minimally dilated ducts was also evident. To assess the size of IPMN on CT images, we carefully inspected the subtle signs corresponding to their features, especially papillary projection into the pancreatic duct, which has been reported to reflect the lateral spreading of low papillary lesions.[24] We examined the accuracy of radiological evaluation such as the size of rIPMN and the rIPMN duct type by comparison with pIPMN size and pIPMN duct type, respectively, using 92 IPMNs other than IC-IPMC. The size of rIPMN was measured fairly accurately and corresponded to the size of pIPMN ± 20% in 92.4% of cases and to the size of pIPMN ± 10% in 67.4% of cases. The rIPMN duct type was correctly evaluated in all but 7% of

IPMN cases. To improve the accuracy of such preoperative evaluation, additional examinations such as endoscopic retrograde cholangiopancreatography, endoscopic US, and magnetic resonance imaging may be helpful to reveal the more detailed characteristics of the lesion, if precise assessment of a laterally spreading lesion is difficult using MDCT. The discrepancy between imaging data and pathological findings may be 1 reason why intraoperative frozen-section analysis is necessary to secure a tumor-free margin.[36]

Historically, there were few reports mentioning about the radiological size of rMPD-type IPMN, and only MPD diameter has been measured.[10,17] The reason may be because the size of rMPD-type IPMN was difficult to be measured radiologically, especially those that are not macroscopically cystic and only accompanied with a diffusely dilated MPD. However, the recent advancement of radiological examinations, especially high-spatial resolution MDCT, makes it possible to evaluate the horizontal extension of intraductal epithelial lesion in the hepatobiliary-pancreatic region. For example, a high diagnostic accuracy of horizontal spreading of hilar cholangiocarcinoma by MDCT is reported.[37] In this study, we deliberately assessed the size of rMPD-type IPMNs, taking into account lateral spreading of papillary lesions, which is reflected on subtle brushlike appearance along the wall of pancreatic ducts (Figs. 2A, B). Measuring the radiological size of all IPMNs on CT images, we could conduct the analysis without separating rBD-type from rMPD/mixed-type IPMN. In addition, our diagnostic score (Table 5A) calculates an extensive MPD-type IPMN (>4 cm in size) as a score of 2 or more and indicates an immediate resection in a surgically fit patient, according to our treatment algorithm (Fig. 4). This is in line with the international consensus guideline,[6] in which all the MPD-type IPMNs are recommended to resection. Thus, actually, the discrimination between BD type and MPD/mixed type is integrated in our scoring system, together with the other 2 predictors (IPMN size and the presence of mural nodule or thick septum).

The number of patients with multifocal IPMNs is relatively small (5 patients) perhaps because the lesion was diagnosed as multiple only when multiple IPMNs were demonstrated pathologically in the resected specimen. For example, when a patient who had 2 suspected IPMN lesions in the pancreatic head and tail underwent pancreaticoduodenectomy and the resected specimen revealed a single IPMN in the pancreatic head, the patient was recognized as having a single IPMN lesion in our analysis because the diagnosis of the tail lesion has not been acquired pathologically.

This study was limited in that it was retrospective and evaluated the predictive ability of CT images for lesions known to be IPMNs. In addition, the study population is composed only of patients who underwent surgical resection. We intend to test our preoperative diagnostic algorithm using another large series of samples or in a prospective study.

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HOW TO DO IT

# Reconstruction of the portal and hepatic veins using venous grafts customized from the bilateral gonadal veins

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**Abstract**
*Background* Surgical resection for pancreatic and hepatic cancer sometimes involves combined resection and reconstruction of the major veins using venous grafts. Autologous venous grafts made from the bilateral gonadal veins (BGVs) have never been utilized or discussed.
*Materials and methods* We reconstructed the portal vein (PV), superior mesenteric vein (SMV), and middle hepatic vein (MHV) using cylindrical or patch grafts customized from the BGVs in two female patients and in one male patient. In order to assess the sexual difference in the availability of the cylindrical graft to replace these major veins, we measured the diameters of the BGVs, PV, SMV, and MHV on computed tomography in 50 male and 50 female patients, and estimated the diameter-ratios (DRs) of the cylindrical graft made from BGVs/PV, SMV, and MHV. We assumed that the cutoff value of the DR would be 0.8, for replacing of major veins using cylindrical grafts.
*Results* The reconstructed PV, SMV, and MHV presented sufficient patency, and the postoperative courses were uneventful. The DRs of BGVs graft/PV, graft/SMV, and graft/MHV were significantly larger in female patients than those in male patients (0.82 vs. 0.54, $p<0.01$, 0.96 vs. 0.61, $p<0.01$, 1.39 vs. 0.95; $p<0.01$) and were larger than 0.8 in 50%, 70%, and 92% in female patients, respectively, and 0%, 8%, and 68% in male patients, respectively.
*Conclusions* The present newly customized cylindrical and patch grafts made from the BGVs showed sufficient feasibility. A cylindrical graft made from the BGVs would be better utilized in female patients than in male patients.

**Keywords** Gonadal vein · Venous graft · Reconstruction · Pancreaticoduodenectomy · Hepatectomy

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## Introduction

Pancreatic and hepatic cancers often infiltrate the portal vein (PV), superior mesenteric vein (SMV), and hepatic veins (HVs), and curative resection of these tumors sometimes involves combined resection of the PV, SMV, and HVs with pancreatectomy and hepatectomy. When the venous defect on the PV or HVs is small, direct suturing would be the most simple and time-preserving method. PV reconstruction during pancreaticoduodenectomy can be performed by direct suturing or direct anastomosis between the PV and SMV without any interposition graft. However, when a direct suturing or direct anastomosis has some risks of kinking, stenosis, or overtension, a venous graft will be necessary. Some authors have reported the usefulness of autologous venous grafts created from the internal jugular vein [1, 2], left renal vein (LRV) [3–9], external iliac vein [10–14], and superficial femoral vein [11]. Others have utilized customized venous grafts made from lesser veins, such as the great saphenous vein [10, 11, 15–17] or right ovarian vein [18], to avoid deficiency or complications associated with sacrificing intrinsic thicker veins. However, the creation of venous grafts using the bilateral gonadal veins (BGVs) has never been reported previously.

In the present paper, we describe three cases of reconstruction of the PV, SMV, and HV, using venous grafts customized from the BGVs. Furthermore, we assessed the sexual difference in the availability of the cylindrical grafts custom-

ized from the BGVs to replace the PV, SMV, and HVs, in terms of the diameter of the graft relative to each vein, based on analysis of 100 computed tomographic (CT) images.

## Materials and methods

We performed resection and reconstruction of the PV and SMV using a patch graft in one female patient and a cylindrical graft in another female patient customized from the BGVs during pancreaticoduodenectomy for pancreatic cancer and reconstruction of the middle hepatic vein (MHV) using a cylindrical graft customized from the BGVs during multiple partial hepatectomies for removal of metastatic rectal cancers in one male patient. Table 1 shows the patient characteristics and the venous diameters on CT scan.

### Techniques of reconstruction of the PV, SMV, and MHV using venous grafts customized from the BGVs

In cases 1 and 2, we performed pancreaticoduodenectomy combined with resection of the PV or SMV for the treatment of pancreatic head cancer. Before resection of the PV or SMV with the specimen, we harvested the BGVs and cut them longitudinally (Fig. 1a). The two pieces from the BGVs were sutured side-by-side intermittently using 6-0 prolene, to obtain a larger sheet (Fig. 1b). In case 1, we sutured the two edges of the defect transversely before patch reconstruction because the defect of the PV was larger than we expected. The sheet graft was patched on the defect with a running suture using 5-0 prolene (Fig. 1c). In case 2, we wrapped the sheet around a 24Fr drain tube longitudinally and sutured it side-by-side intermittently using 6-0 prolene, to make a cylindrical graft. The finished graft was interposed in the venous defect for reconstruction of the SMV with running sutures using 6-0 prolene (Fig. 1d).

In case 3, a male patient had six metastatic hepatic tumors from rectal cancer, and one of these tumors involved the MHV. He underwent preoperative systemic chemotherapy using irinotecan and oxaliplatin, intravenous fluorouracil, and leucovorin for 1 year and additional hepatic arterial infusion therapy with fluorouracil. We performed six partial hepatectomies and combined with resection of the MHV. On CT scan, the diameter ratio (DR) of the sum of the diameters of the BGVs to the diameter of the MHV (BGVs graft/MHV) was 0.72 (Table 1), the cylindrical graft made from the two pieces of the BGVs was supposed to be insufficient to replace the MHV. After dividing the liver parenchyma around the MHV, we harvested the right GV, 7.0 cm in length, and the left GV, 5.0 cm in length, and cut them longitudinally (Fig. 1e). We divided the right GV into two half-length pieces, 3.5 cm in length, and divided left GV into two pieces, 3.5 cm×1.0 cm in size. We wrapped the three pieces of the BGVs, 3.5 cm in length, around a 24Fr drain tube longitudinally and sutured them side-by-side intermittently using 7-0 prolene to make a cylindrical graft, with a diameter of 1.0 cm and a length of 3.5 cm. We segmentally removed the MHV for 3 cm in length and interposed the cylindrical graft with running suture using 6-0 prolene (Fig. 1f). We did not perform anticoagulant therapy in these three patients.

### Analysis of the diameters of the BGVs, PV, SMV, and HVs on CT images

The clinical records and CT images of the patients who visited our outpatient clinic from August 2007 to July 2008 were reviewed retrospectively. Patients who had history of abdominal surgery, gynecologic surgery, or portal hypertension with blood platelet counts less than 100,000 per microliter were excluded from this study. The underlying disease in the 100 patients included pancreatic head cancer ($n$=42), pancreatic body or tail cancer ($n$=13), distal bile duct cancer ($n$=3), hilar bile duct cancer ($n$=6), gallbladder cancer ($n$=1), duodenal cancer ($n$=1), hepatocellular carcinoma ($n$=14), intrahepatic cholangiocarcinoma ($n$=8), intraductal papillary mucinous tumor of pancreas ($n$=2), pancreatic endocrine tumor ($n$=4), retroperitoneal tumor ($n$=3), other hepatic tumor ($n$=2), and pancreatitis (n=1). There were 50 men and 50 women, with a mean age of 63 years (range, 33–81 years). A 16-row multidetector scanner (Aquilion V-detector, Toshiba Medical Systems, Tokyo, Japan) was used in all the patients with intravenous contrast injection. CT scans were obtained during the arterial phase (40-s delay), portal venous phase (70-s delay), and equilibrium phase (3-min delay) after intravenous administration, at section thicknesses of 1 and 5 mm and intervals of 1 and 5 mm through the abdomen and pelvis.

We measured the maximum diameters of the BGVs, PV, SMV, right hepatic vein (RHV), MHV, and left hepatic vein (LHV) in the transverse images in each patient. The diameters of the PV and SMV were measured at the level of the superior and inferior borders of the pancreas, respectively. The diameters of the three HVs were measured at the confluence with the inferior vena cava.

We studied the sexual differences in the diameters of the BGVs, PV, SMV, and HVs, and also examined the sexual differences in the DRs of the sum of the diameters of the BGVs to the diameter of the PV, SMV, and HVs (BGVs graft/PV, graft/SMV, and graft/HVs), in order to investigate whether cylindrical venous grafts prepared from the BGVs were suitable for bridging of the venous defect in the PV, SMV, and HVs. We assumed that the acceptable cutoff value of the DR of the graft/PV, graft/SMV, or graft/HVs would be 0.8, for safe replacing of the PV, SMV, or HVs using the cylindrical graft made from the BGVs.

Data were entered into a computer database and statistically analyzed using SPSS for Windows (version

**Table 1** Patient characteristics and the venous diameters on computed tomography scan in three patients undergoing venous reconstruction using the bilateral gonadal veins

| Case | Age/ sex | Disease | Tumor size (mm) | Involved vein | Involved length (mm) | Diameters on CT scan (mm) | | | | | | Diameter-ratio | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PV | SMV | MHV | RGV | LGV | Sum of BGVs | BGVs/ MHV | BGVs/ PV | BGVs/ SMV |
| 1 | 66/F | PC | 33 | PV | 30 | 11.7 | 7.3 | – | 2.9 | 4.5 | 7.4 | 0.63 | 1.01 | – |
| 2 | 50/F | PC | 40 | SMV | 35 | 12.2 | 7.5 | – | 3.4 | 3.4 | 6.8 | 0.55 | 0.89 | – |
| 3 | 59/M | LM | 40 | MHV | 30 | – | – | 9.4 | 3.5 | 3.3 | 6.8 | – | – | 0.72 |

*PC* pancreatic invasive cancer, *LM*, liver metastasis, *PV* portal vein, *SMV* superior mesenteric vein, *MHV* middle hepatic vein, *CT* scan computed tomography scan, *RGV* right gonadal vein, *LGV* left gonadal vein, *BGVs* bilateral gonadal veins, *BGVs/PV* the diameter-ratio of the sum of the BGVs to the PV, *BGVs/SMV* the diameter-ratio of the sum of the BGVs to the SMV, *BGVs/MHV* the diameter-ratio of the sum of the BGVs to the MHV

11.5; SPSS, Chicago, IL, USA). The summarized data were formatted as mean±standard deviation (SD). Statistical analysis was evaluated using the paired Student's *t* test for parametrically distributed data and the Wilcoxon matched-pair signed-rank test for nonparametrically distributed data. $P<0.05$ was considered to be statistically significant.

## Results

All of the three patients undergoing reconstruction of the PV, SMV, and MHV using venous grafts customized from the BGVs had uneventful perioperative courses. Table 2 shows the surgical results of the three patients. Good patency

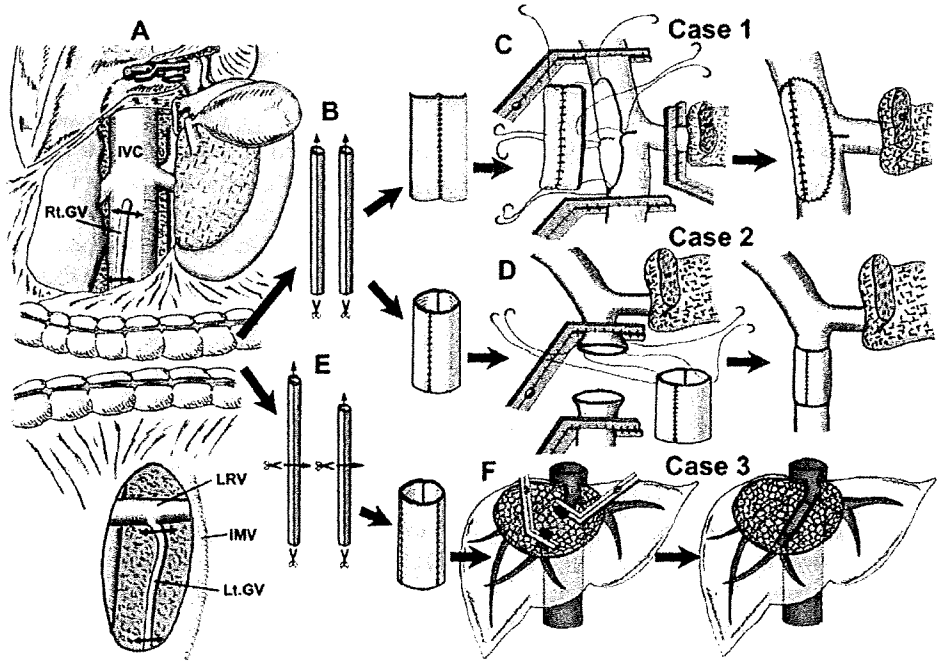


**Fig. 1** Schematic illustration of reconstruction of the portal vein (PV), superior mesenteric vein (SMV), and middle hepatic vein (MHV) using grafts customized from the bilateral gonadal veins (BGVs). *A* The proximal side of the BGVs was sacrificed. *B* Sacrificed BGVs were cut longitudinally. The two pieces obtained were sutured intermittently side-by-side using 6-0 prolene, to make a sheet graft. *C* The obtained sheet graft was patched on to the defect of the PV with a running suture using 5-0 prolene. Before patching the graft, both edges of the PV defect were sutured for a length of 1 cm to reduce the size of the defect. *D* The obtained sheet was rolled around a 24Fr drain tube and sutured side-by-side intermittently using 6-0 prolene. The finished cylindrical graft was interposed to reconstruct the SMV with a running suture using 6-0 prolene. *E* We harvested the right GV, 7.0 cm in length, and the left GV, 5 cm in length, and cut them longitudinally. We divided right GV into two equal parts, 3.5 cm in length, and divided left GV into two parts, 3.5 cm×1.0 cm in size, respectively. *F* We wrapped these three pieces with length of 3.5 cm around a 24Fr drain tube longitudinally and sutured them side-by-side intermittently using 7-0 prolene to make a cylindrical graft. We interposed the cylindrical graft in the venous defect for reconstruction of the MHV with running suture using 6-0 prolene. *IVC* inferior vena cava, *Rt.GV* right gonadal vein, *LRV* left renal vein, *IMV* inferior mesenteric vein, *Lt.GV* left gonadal vein

of the reconstructed veins was confirmed in follow-up CT scans, 5, 1, and 1 months after the surgery, respectively. None of the patients developed any complication associated with sacrificing the BGVs.

The BGVs, PV, SMV, and HVs were visualized in all the 100 patients on CT images. The right GV joined to the right renal vein in six patients and to the inferior vena cava in 94 patients. The left GV was joined to the LRV in all patients. Table 3 shows the sexual differences in the diameters of the right, left, and BGVs, PV, SMV, and HVs. The diameters of right, left, and BGVs were significantly larger in female patients than in male patients ($p$=0.02, <0.01, <0.01). On the other hand, the diameters of the PV, SMV, and MHV were significantly smaller in female patients than in male patients ($p$<0.01, <0.01, <0.01). There were no significant differences between the male and female patients in the diameter of the RHV and LHV. The left GV was significantly larger than the right GV in female patients ($p$<0.01), while there was no significant difference in the diameter between the right and left GVs in male patients ($p$=0.50).

Figure 2 shows the box plots of the DRs of the sum of the diameters of the BGVs to the diameters of the PV, SMV, and MHV. The DRs of BGVs graft/ PV, graft/SMV, and graft/MHV were significantly greater in female patients than in male patients (DR of BGVs graft/PV, 0.82±0.22 vs. 0.54±0.09; DR of BGVs graft/SMV, 0.94±0.26 vs. 0.61± 0.13; DR of BGVs graft/MHV, 1.39±0.53 vs. 0.95±0.26; $p$<0.01, <0.01, <0.01).

The DRs of BGVs graft/PV and graft/SMV were larger than 0.8 in 50% and 70% in female patients, respectively, and 0% and 8% in male patients, respectively. The DRs of BGVs graft/MHV were larger than 0.8 in 92% in female patients and 68% in male patients.

## Discussion

In this report, we present the usefulness of newly developed patch and cylindrical grafts customized from the BGVs for reconstruction of the PV, SMV, or MHV. The BGVs were easily and safely excised with length of approximately 6 cm from the same surgical field without making additional incision or adverse effect. To the best of our knowledge, there has been only one report of the use of a venous patch graft made from the right ovarian vein after PV or HV wedge resection in female patients [18]. None of the three patients developed any complication associated with sacrificing the BGVs. We believe that the side effect of sacrificing the BGVs is minimal, but there are some reports of gonadal vein thrombosis presenting with lower abdominal pain [19, 20]. This issue should be further evaluated.

Analysis of the diameters on CT images revealed that cylindrical grafts prepared from two pieces of the BGVs may be too thin in about half of female patients and almost all of male patients for replacing of the PV or SMV, if we assume that the required DR of the graft might be 0.8 for safe replacing of the intrinsic veins. Cylindrical grafts prepared from the BGVs may be sufficient in almost all of female patients and about two thirds of male patients for replacing of the HVs. In case 3, as the DR of the BGVs graft/MHV was less than 0.8, we replaced a venous graft from three pieces of the BGVs and obtained a sufficient caliber. These results suggest that cylindrical venous grafts made from the BGVs could be better utilized in female patients than in male patients. It should be important to estimate the DR of the grafts/PV, graft/SMV, or graft/HV on preoperative CT scans and to plan the method of resection and reconstruction of the major intrinsic veins. If a cylindrical graft is supposed to be too thin for replacing a major vein on preoperative CT scan, (1) patch reconstruction using a sheet graft, 2) reconstruction using a cylindrical graft made from three pieces of BGVs, or 3) reconstruction using other thicker veins, would be alternatives for safe reconstruction of major veins.

In the present study, the left GV was significantly thicker than the right GV in the female patients, but not in the male patients. Hiromura et al. [21] reported that parous women had wider ovarian veins than nulliparous woman, and reflux of contrast medium from the LRV into the left ovarian vein was found in 44% (48/110) of parous women. Rebner M et al. [22] suggested that the increased venous blood flow during pregnancy might account for the enlargement of the GVs in postpartum patients. Goken et al. [23] reported that the right

**Table 2** Surgical results in three patients undergoing venous reconstruction using the bilateral gonadal veins

| Case | Type of the graft | Size of the sheet (mm) | Diameter of the graft (mm) | Operation time (min) | Blood loss (ml) | Graft time (min) | Clamping time (min) | Hospital stay (days) | Outcome | Survival time (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Patch | 22×40 | NA | 590 | 1,100 | 35 | 53 | 20 | Alive | 5 |
| 2 | Cylinder | 21×30 | 7 | 620 | 660 | 32 | 35 | 35 | Died of recurrence | 17 |
| 3 | Cylinder | 35×30 | 10 | 780 | 1,510 | 50 | 45 | 17 | Alive | 2 |

*graft time* time required for modifying the venous graft, *clamping time* clamping time required for reconstruction of the portal vein or hepatic vein, *NA* not available

**Table 3** Comparison of the diameters of the right, left, and bilateral gonadal veins, portal vein, superior mesenteric vein, right hepatic vein, middle hepatic vein, and left hepatic vein between male and female patients

| Type of the vein | Mean diameter of the vein (mm, mean±SD) | | *p* Value |
|---|---|---|---|
| | Female ($n$=50) | Male ($n$=50) | |
| Right gonadal vein | 3.9±0.9 | 3.6±0.6 | 0.02 |
| Left gonadal vein | 5.3±2.0 | 3.6±0.8 | <0.01 |
| Sum of bilateral gonadal veins | 9.3±2.5 | 7.2±1.2 | <0.01 |
| Portal vein | 11.4±1.1 | 13.7±1.6 | <0.01 |
| Superior mesenteric vein | 9.5±1.4 | 12.0±1.5 | <0.01 |
| Right hepatic vein | 8.2±2.2 | 8.3±2.0 | 0.96 |
| Middle hepatic vein | 7.1±1.5 | 7.9±1.7 | <0.01 |
| Left hepatic vein | 7.8±1.8 | 8.2±2.1 | 0.31 |

GV was enlarged on the CT in patients with mesenteric varices or portal hypertension. Although enlargements of the GVs may be associated with many conditions including postpartum period, pregnancy, and portal hypertension, our results clearly indicate the tendency toward enlargement of the GVs in female subjects.

The superficial femoral vein, internal jugular vein, and external iliac vein are useful alternative sources for cylindrical grafts needing no modification, but sacrificing these veins may be associated with postoperative venous congestion, although it is usually compensated. The LRV provides a graft with good caliber and is easily accessible without additional incision; however, transient renal dysfunction has been reported after ligation or transection of the LRV [6, 8, 24], LRV grafts may not be feasible in patients with poor renal or general condition. Although utility of synthetic grafts has been reported, this method might be associated with graft infection and subsequent loss [25]. The advantages of venous reconstruction using BGVs would be (1) the graft is autologous, (2) easy accessibility without additional incision, and (3) safety without any complication associated with sacrificing BGVs. The disadvantage would be that this method is time-consuming, requiring 30 min for making a cylindrical graft. Our method could be utilized even in poor risk patients.

What would be the acceptable DRs of the graft/PV, graft/SMV, or graft/HVs for bridging of the venous defect in the PV, SMV, or HVs? This is a crucial question. In case 2, the DR of the BGVs graft/SMV was 0.89, and the patency of the reconstructed SMV was confirmed at 1 month after the surgery. Therefore, we assumed that the acceptable DR of the graft/PV, graft/SMV, or graft/HV on preoperative CT would be no less than 0.8. We believe that DR of 0.8 would be a safe and acceptable threshold for replacing PV or HV without stenosis or obstruction using a cylindrical graft made from BGVs, but we must further accumulate the data and look for a better cutoff value. In case 3, the DR of the BGVs graft/MHV was 0.72; therefore, we made a thicker cylindrical graft using three pieces of BGVs, and the DR of the graft/MHV increased to 1.10. If we have rolled the three

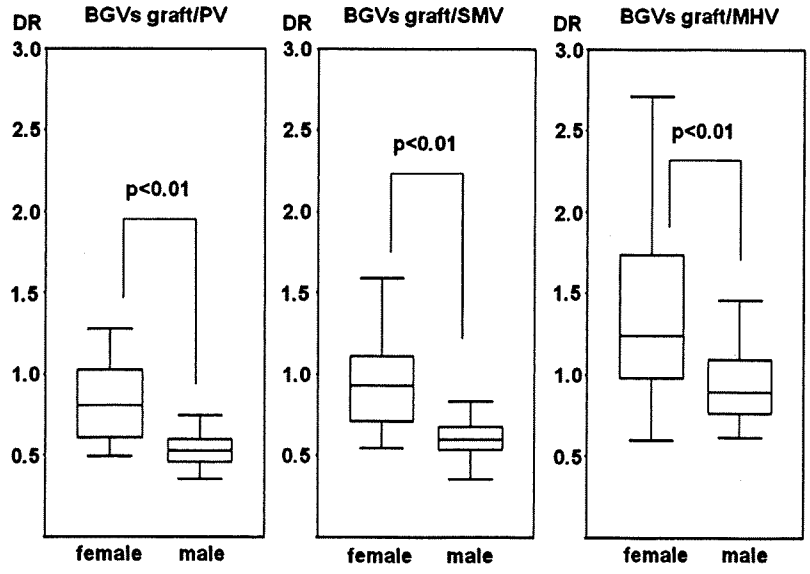


**Fig. 2** Box plots of the diameter-ratios (DRs) of the sum of the bilateral gonadal veins divided by the portal vein, superior mesenteric vein, and middle hepatic vein. Diameter-ratio (DR)=The sum of the BGVs/PV, SMV, and MHV. *DR* diameter-ratio, *PV* portal vein, *BGVs* bilateral gonadal veins, *SMV* superior mesenteric vein, *MHV* middle hepatic vein