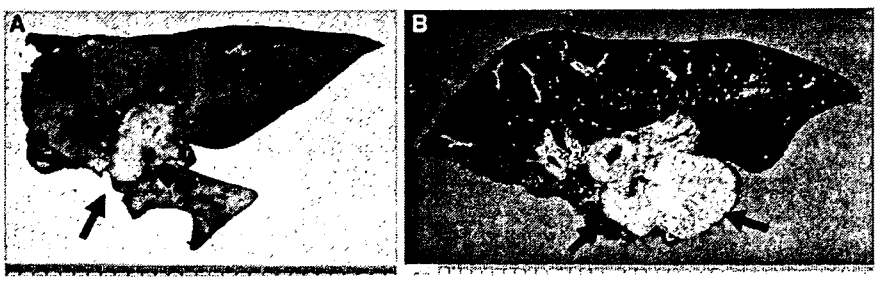



FIG. 2. Representative case of hilar bile duct cancer (A) and intrahepatic cholangiocarcinoma involving the hepatic hilus (B) on the slice section of resected specimen. Arrows indicate tumor.

adjuvant therapy such as chemotherapy, radiotherapy, or chemoradiotherapy was not adopted until tumor recurrence was definitively diagnosed.

### Statistical Analysis

The results are expressed as median values, with the respective ranges indicated within square brackets. The relationship between the postoperative morbidity and the dichotomous variables was evaluated by chi-square analysis or Fisher's test, whichever was appropriate. The statistical significance of continuous variables was determined using the Mann-Whitney test. Patient survival was calculated using the Kaplan-Meier method, including deaths from all causes. Univariate comparisons of the survival curves were performed using the log-rank test. Multivariate regression analysis (backward elimination method) was performed using the Cox proportional hazards model,[19] and variables associated with $P < .10$ were entered into the final model. Results were considered significant when the $P$ values were less than .05. The statistical analyses were performed using a statistical analysis software package (SPSS 11.5, SPSS Inc. Chicago, IL).

## RESULTS

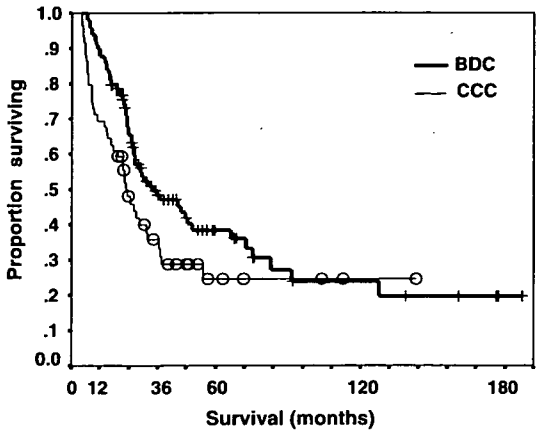
The patients' overall 1-, 3-, and 5-year survival rates were 81.0%, 43.7%, and 33.4%, respectively. The median survival was 28.4 (4.1–187.1) months, and the median follow-up time was 25.2 (4.1–187.1) months. Ninety-seven patients died of tumor recurrence, and two patients died without evidence of tumor recurrence. The remaining 59 patients are currently alive; 12 have recurrence, and 47 have no sign of recurrence at the time of writing.

The patient characteristics and preoperative variables are summarized in Table 1. The six clinicopathological variables were compared. Preoperative biliary drainage was performed significantly more frequently in BDC patients ($P < .001$). Serum CA19-9 levels were significantly higher in CCC patients ($P = .006$). There were no significant differences in other variables between BDC and CCC patients. There were no in-hospital deaths in the BDC group, but two patients with CCC died in hospital (CCC mortality rate, 3.4%; overall mortality rate, 1.3%). Eighty-three patients (52.5%) developed postoperative morbidity. There were no statistically significant differences in mortality or morbidity between the two groups (Table 2).

The overall 1-, 3-, 5-year survival rates and median survival time of BDC patients were 87.9%, 48.4%, 38.4 %, and 33.7 months, respectively. The overall 1-, 3-, 5-year survival rates and median survival time of CCC patients were 69.5%, 35.8%, 24.5 %, and 22.7 months, respectively. There was a significant difference in the overall survival between BDC and CCC patients ($P = .033$) (Fig. 3). Figures 4**A** and 4**B** show the survival curves of BDC and CCC patients by UICC staging. Significant differences were noted between stages I and II ($P = .0023$), stages I and III ($P = .0453$), and stages I and IV ($P = .0006$) in BDC patients (Fig. 4**A**). Significant differences were also noted between stages I and IV ($P = .0039$), stages II and IV ($P = .0112$), and stages III and IV ($P = .0285$) in CCC patients (Fig. 4**B**). For any given stage, there was no significant difference in survival between BDC and CCC patients: stage I ($P = .5016$), II ($P = .3316$), III ($P = .9584$), and IV ($P = .1387$).

The surgical procedures and operative variables are summarized in Table 2. Hepatopancreatoduodenectomy (HPD)[20] ($P = .012$), PVE ($P = .005$), and right-sided hepatectomy ($P = .033$) were performed significantly more frequently in BDC patients. There were no other significant differences in the surgical procedures or operative variables between the BDC and CCC patients.

The 11 histopathological variables were compared (Table 3). Well differentiated or papillary adenocarcinoma ($P = .034$) and positive proximal ($P = .046$)




No. at risk

| | | | | | |
|---|---|---|---|---|---|
| BDC | 99 | 87 | 35 | 16 | 6 |
| CCC | 59 | 41 | 15 | 5 | 1 |

FIG. 3. The survival curves for hilar bile duct cancer (BDC) patients and intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC) patients. The overall 1-, 3-, 5-year survival rates, and median survival time of BDC patients were 87.9%, 48.4%, 38.4 %, and 33.7 months, respectively. The overall 1-, 3-, 5-year survival rates, and median survival time of CCC patients were 69.5%, 35.8%, 24.5 %, and 22.7 months, respectively. There was a significant difference in the overall survival between BDC and CCC patients ($P$ = .0333).

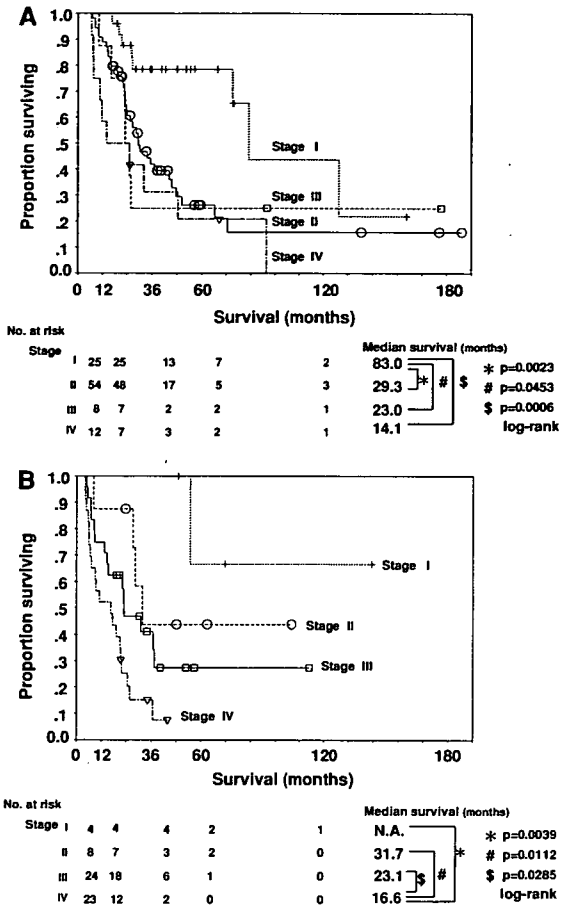



FIG. 4 Survival curves. (A) BDC patients by UICC pathological stage. Significant differences were noted between stages I and II ($P$ = .0023), stages I and III ($P$ = .0453), and stages I and IV ($P$ = .0006). (B) The survival curves of CCC patients by UICC pathological stage. Significant differences were noted between stages I and IV ($P$ = .0039), stages II and IV ($P$ = .0112), and stages III and IV ($P$ = .0285).

or distal ($P$ = .028) bile duct margins were significantly more frequent in BDC patients. On the other hand, resected major portal vein invasion ($P$ = .001) and moderate to severe venous invasion ($P$ = .004) were significantly more frequent in CCC patients. There were no significant differences between BDC and CCC patients in the remaining six histopathological variables.

The 9 clinical and 11 histopathological risk factors possibly related to survival in BDC patients were analyzed by the log-rank test (Table 4). Male gender ($P$ = .040), preoperative biliary drainage ($P$ = .005), and an ICG R15 over 10% ($P$ = .030) were significant clinical risk factors in BDC patients. Histologic differentiation ($P$ = .010), depth of tumor invasion ($P$ = .005), lymph node involvement ($P$ < .001), resected major portal vein invasion ($P$ = .009), venous invasion ($P$ = .039), and nervous system invasion ($P$ = .004) were significant histopathological risk factors in BDC patients.

The 8 clinical and 12 histopathological risk factors possibly related to survival in CCC patients were analyzed by the log-rank test (Table 5). Serum CA 19-9 ($P$ = .006), CEA level ($P$ = .002), and red blood cell transfusion requirement ($P$ < .001) were significant clinical risk factors in CCC patients. Macroscopic tumor type ($P$ = .004), resected major portal vein invasion ($P$ = .011), T-category ($P$ = .001), lymph node involvement ($P$ = .016), lymphatic system invasion ($P$ = .014), venous invasion ($P$ = .017), nervous system invasion ($P$ = .036), presence of intrahepatic daughter nodules ($P$ = .003), and cancer-positive proximal bile duct margin ($P$ = .003) were significant histopathological risk factors in CCC patients.

Multivariate analysis using the Cox proportional hazard model identified the curative resection with cancer-free margin (R0) (P = .024, odds ratio 1.862), the histologic type (well differentiated or papillary adenocarcinoma) ($P$ = .011, odds ratio 2.135), and the absence of lymph node involvement ($P$ < .001, odds ratio 3.314) as independent factors that contributed to

TABLE 3. *Histopathological variables*

| Variable | | BDC ($n$ = 99) | CCC ($n$ = 59) | $P$ value |
|---|---|---|---|---|
| Histologic differentiation | Well, papillary | 36 (36%) | 12 (20%) | .034 |
| T-category | 1, 2 | 40 (40) | 26 (44) | |
| Lymph node metastasis | Present | 47 (47) | 36 (61) | |
| Invasion of the resected major portal vein | Present | 26 (26) | 31 (53) | .001 |
| Invasion of the lymphatic system | Absent or slight | 62 (63) | 29 (49) | |
| Invasion of the venous system | Absent or slight | 65 (66) | 25 (42) | .004 |
| Invasion of the nervous system | Absent or slight | 32 (32) | 18 (31) | |
| Histological stage | I, II | 79 (80) | 12 (20) | < .001 |
| Proximal ductal margin | Positive | 29 (29) | 9 (15) | .046 |
| Distal ductal margin | Positive | 17 (17) | 3 (5) | .028 |
| Dissected periductal margin | Positive | 13 (13) | 10 (17) | |
| R0 resection | Achieved | 58 (59) | 43 (73) | |

Percentage are described in parentheses.

prolonged survival in BDC patients. On the other hand, the absence of intrahepatic daughter nodules ($P$ < .001, odds ratio 2.318), preoperative serum CEA level of 2.9 ng/mL or less ($P$ = .005, odds ratio 2.606), red blood cell transfusion requirement ($P$ = .016, odds ratio 2.614), absence or slight degree of lymphatic system invasion ($P$ < .001, odds ratio 4.577), and cancer-negative proximal bile duct margin ($P$ = .003, odds ratio 7.398) were identified as independent factors that contributed to prolonged survival in CCC patients (Table 6).

## DISCUSSION

The clinical impact of differentiating between BDC and CCC has not been clarified. In this setting, our present study is the first large, single-center series that has addressed the prognostic factors for BDC and CCC separately. Nakeeb et al.[21] evaluated the surgical outcome of cholangiocarcinoma divided into three categories: intrahepatic, perihilar, and distal cholang iocarcinoma. Their classification appears to be reasonable with respect to the choice of surgical procedure: hepatectomy for intrahepatic cholangiocarcinoma, hepatobiliary resection for perihilar cholangiocarcinoma, and the Whipple procedure for distal cholangiocarcinoma. Although perihilar cholangiocarcinoma can be divided into BDC and CCC based on the anatomical origin of the tumor, a substantial number of reports have described the surgical outcome of hilar cholangiocarcinoma, which have likely included CCC patients. We previously reported the safety and short-term outcome of major hepatobiliary resection for perihilar cholangiocarcinoma.[14] In the present study, we performed a prognostic analysis of perihilar cholangiocarcinoma patients treated with major hepatobiliary resection to delineate the characteristics of long-term survivors and to assess the impact of differentiating between BDC and CCC.

The overall survival of BDC patients was significantly better than that of CCC patients (Fig. 1, $P$ = .033). This difference is potentially caused by a different distribution of the pathological stages in this study; CCC patients had a higher proportion of stage III or IV disease (74.6%) than BDC patients (25.3%, $P$ < .001). In fact, there was no significant difference in the overall survival between BDC and CCC patients with the same stage. However, the validity of using the UICC staging system based on the TNM classification of extrahepatic bile duct cancer for BDC and liver cancer for CCC to compare the two groups might be questioned. Many of the possible risk factors that were analyzed are similar for both BDC and CCC, though on univariate analysis, only a few factors were significant predictors for both. On multivariate analysis, no significant independent prognostic factors were common for both BDC and CCC. Thus, BDC and CCC appear to show independent biological behaviors. Therefore, differentiating between BDC and CCC would have an impact on our ability to predict postoperative survival based on their independent prognostic factors.

BDC is typically associated with thickness or irregularity of the bile duct wall with or without involvement of adjacent liver parenchyma or portal structures. CCC is frequently associated with tumor bulk with or without invasion to Glisson's capsule on imaging studies; both BDC and CCC may show intraductal tumor extension.[17] Tumor bulk might be related to the higher CEA and CA19-9 levels seen in CCC than in BDC. Nevertheless, precise preoperative differentiation between BDC and CCC using various diagnostic imaging studies or clinical manifestation is

**TABLE 4.** *Possible clinical and pathological risk factors for survival in BDC (univariate analysis)*

| Factors | No. of patients | Survival rate (%) 3-year | 5-year | Median survival (months) | *P* value |
|---|---|---|---|---|---|
| Overall | 99 | 48.4 | 38.4 | 33.7 | |
| Age (median: 64 years) | | | | | |
| ≤64 | 50 | 56.7 | 41.6 | 47.6 | |
| >64 | 49 | 39.6 | 35.6 | 29.3 | |
| Gender | | | | | .040 |
| Male | 69 | 43.6 | 31 | 30.1 | |
| Female | 30 | 58.8 | 53.9 | 72.7 | |
| Biliary drainage | | | | | .005 |
| Not performed | 22 | 80.7 | 68.7 | 72.7 | |
| Performed | 77 | 38.5 | 28.8 | 26.7 | |
| ICG R15 (normal range; ≤10%) | | | | | .030 |
| ≤10 | 62 | 54.4 | 45.8 | 47.6 | |
| >10 | 37 | 38.2 | 26.4 | 26.5 | |
| CA19-9 (median: 101 U/mL) | | | | | |
| ≤101 | 50 | 48.3 | 38.0 | 33.7 | |
| >101 | 49 | 48.7 | 39.6 | 35.5 | |
| CEA (median: 2.5 ng/mL) | | | | | |
| ≤2.5 | 53 | 41.5 | 27.8 | 26.7 | |
| >2.5 | 46 | 55.8 | 51.9 | 66.4 | |
| With PD | | | | | |
| Yes | 10 | 41.1 | 41.1 | 32 | |
| No | 89 | 49.1 | 38.3 | 35.5 | |
| With VR | | | | | |
| Yes | 24 | 41.9 | 35.9 | 28.3 | |
| No | 75 | 50.4 | 39.1 | 37.2 | |
| Red blood cell transfusion | | | | | |
| Performed | 34 | 39.2 | 31.4 | 28.3 | |
| Not performed | 65 | 54 | 43 | 44.3 | |
| Macroscopic type of the tumor | | | | | |
| Polypoid | 9 | 63.5 | 47.6 | 45.5 | |
| Nodular or infiltrative | 90 | 47.0 | 37.7 | 32.0 | |
| Histologic differentiation | | | | | |
| Well or papillary | 36 | 60.0 | 56.3 | 83.0 | .010 |
| Others | 63 | 42.0 | 25.9 | 26.5 | |
| Depth of tumor invasion | | | | | |
| Mucosal, fibromuscle layer | 8 | 100.0 | 100.0 | N.A. | .005 |
| Subserosal or more | 91 | 43.8 | 33.7 | 29.3 | |
| T category | | | | | |
| 1, 2 | 40 | 59.6 | 59.6 | 83.0 | |
| 3, 4 | 59 | 41.1 | 25.0 | 29.1 | |
| Lymph node involvement | | | | | <.001 |
| Negative | 52 | 67.3 | 58.4 | 75.2 | |
| Positive | 47 | 27.7 | 15.9 | 23.1 | |
| Invasion of the resected portal vein | | | | | .009 |
| Absent | 73 | 55.7 | 51.1 | 66.4 | |
| Present | 26 | 30.8 | 13.2 | 23.5 | |
| Invasion of the lymphatic system | | | | | |
| Absent or slight | 62 | 54.4 | 46.6 | 45.5 | |
| Moderate to marked | 37 | 38.8 | 25.9 | 29.3 | |
| Invasion of the venous system | | | | | .039 |
| Absent or slight | 65 | 57.4 | 46.0 | 47.6 | |
| Moderate to marked | 34 | 31.2 | 23.4 | 25.2 | |
| Invasion of the nervous system | | | | | .004 |
| Absent or slight | 32 | 70.5 | 60.6 | 127.7 | |
| Moderate to marked | 67 | 38.2 | 28.3 | 26.0 | |
| Proximal ductal margin | | | | | |
| Negative | 70 | 54.1 | 41.1 | 45.5 | |
| Positive | 29 | 32.6 | 32.6 | 25.2 | |
| R0 resection | | | | | |
| Achieved | 58 | 57.2 | 44.4 | 45.5 | |
| Not achieved | 41 | 35.1 | 30.1 | 29.9 | |

ICGR15 indicates indocyanine green retention value at 15 minutes; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembrionic antigen; PD, pancreatoduodenectomy; VR, vascular (hepatic artery, portal vein or inferior vena cava) resection and reconstruction; N.A., not available.

**TABLE 5.** *Possible clinical and pathological risk factors for survival in CCC (univariate analysis)*

| Factors | No. of patients | Survival rate (%) 3-year | 5-year | Median survival (months) | *P* value |
|---|---|---|---|---|---|
| Overall | 59 | 35.8 | 24.5 | 22.7 | |
| Age (median, 66 years) | | | | | |
| ≤66 | 33 | 29.2 | 25.1 | 22.1 | |
| >66 | 26 | 43.8 | 24.7 | 28.4 | |
| Gender | | | | | |
| Male | 37 | 37.6 | 28.2 | 21.5 | |
| Female | 22 | 34.1 | 21.9 | 24.7 | |
| Biliary drainage | | | | | |
| Not performed | 43 | 36.6 | 30.5 | 25.9 | |
| Performed | 16 | 33.3 | 11.1 | 17.5 | |
| ICG R15 (normal range, ≤10%) | | | | | |
| ≤10 | 43 | 36.7 | 30.1 | 32.1 | |
| >10 | 16 | 34.7 | 13 | 25.9 | |
| CA19-9 (median, 306 IU/mL) | | | | | .006 |
| ≤306 | 30 | 50.4 | 35 | 37 | |
| >306 | 29 | 21.1 | 14.1 | 14.8 | |
| CEA (median, 2.9 mg/dL) | | | | | .002 |
| ≤2.9 | 30 | 50.4 | 38.1 | 36.7 | |
| >2.9 | 29 | 20.6 | 10.3 | 14.8 | |
| With VR | | | | | |
| Yes | 21 | 37.1 | 14.9 | 23.1 | |
| No | 38 | 34.9 | 27.9 | 22.1 | |
| Red blood cell transfusion | | | | | <.001 |
| Performed | 26 | 11.5 | 3.9 | 17.5 | |
| Not performed | 33 | 58.4 | 45.9 | 54.9 | |
| Macroscopic type of the tumor | | | | | .004 |
| Mass-forming | 44 | 25.8 | 12.3 | 17.5 | |
| Periductal or intraductal | 15 | 6.6 | 56.5 | N.A. | |
| Serosal invasion | | | | | |
| Positive | 7 | 21.4 | 0 | 7 | |
| Negative | 52 | 37.6 | 27.6 | 23.1 | |
| Histologic differentiation | | | | | |
| Well or papillary | 12 | 41.7 | 31.3 | 25.9 | |
| Others | 47 | 34.4 | 24.1 | 22.1 | |
| Invasion of resected major portal vein | | | | | .011 |
| Absent | 29 | 49 | 38.5 | 31.7 | |
| Present | 30 | 22.7 | N.A. | 17.5 | |
| T category | | | | | .001 |
| 1, 2 | 26 | 55.3 | 47.4 | 54.9 | |
| 3, 4 | 33 | 20.2 | N.A. | 17.5 | |
| Lymph node involvement | | | | | .016 |
| Negative | 23 | 50.6 | 37.5 | 37.4 | |
| Positive | 36 | 26.8 | 17.9 | 17.5 | |
| Invasion of the lymphatic system | | | | | .014 |
| Absent or slight | 29 | 52.6 | 33.8 | 36.7 | |
| Moderate to marked | 30 | 19 | 19 | 16.6 | |
| Invasion of the venous system | | | | | .017 |
| Absent or slight | 25 | 45.4 | 40.3 | 31.1 | |
| Moderate to marked | 34 | 28.9 | 0 | 16.6 | |
| Invasion of the nervous system | | | | | .036 |
| Absent or slight | 18 | 60.2 | 40.1 | 54.9 | |
| Moderate to marked | 41 | 25 | 16.7 | 21.5 | |
| Intrahepatic daughter nodule | | | | | .003 |
| Absent | 42 | 44.4 | 31.3 | 31.1 | |
| Present | 17 | 14.1 | 7.1 | 11.1 | |
| Proximal bile ductal margin | | | | | .003 |
| Negative | 50 | 40.5 | 29.8 | 27.2 | |
| Positive | 9 | 11.1 | 0 | 9.3 | |
| R0 resection | | | | | |
| Achieved | 42 | 40.6 | 29.5 | 27.2 | |
| Not achieved | 17 | 23.2 | N.A. | 21.5 | |

ICGR15 indicates indocyanine green retention value at 15 minutes; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembrionic antigen; VR, vascular (hepatic artery, portal vein or inferior vena cava) resection and reconstruction; N.A., not available.

**TABLE 6.** *Risk factors associated with postoperative survival in patients with perihilar cholangiocarcinoma (Cox Multivariate Regression Analysis)*

| Variable | β | SE | *P* value | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| **BDC patients** | | | | | |
| R0 resection | 0.622 | 0.275 | .024 | 1.862 | 1.085–3.194 |
| Histologic differentiation (well, papillary versus others) | 0.759 | 0.300 | .011 | 2.135 | 1.186–3.844 |
| Lymph node involvement | 1.198 | 0.282 | <.001 | 3.314 | 1.906–5.763 |
| **CCC patients** | | | | | |
| Intrahepatic daughter nodule | 0.841 | 0.239 | <.001 | 2.318 | 1.450–3.705 |
| Preoperative serum CEA level over 2.9 ng/mL | 0.958 | 0.341 | .005 | 2.606 | 1.337–5.080 |
| Red blood cell transfusion requirement | 0.961 | 0.399 | .016 | 2.614 | 1.195–5.719 |
| Invasion of the lymphatic system | 1.521 | 0.423 | <.001 | 4.577 | 1.997–10.494 |
| Proximal bile duct margin | 2.001 | 0.673 | .003 | 7.398 | 1.976–27.688 |

$P < 0.1$ was set as the cut-off for variable elimination.

sometimes difficult. Actually, in 12 of 59 cases (20%) finally diagnosed as CCC, 17 of 99 cases (17%) finally diagnosed as BDC, it was not easy to discriminate between CCC and BDC by the review of pathologist. In our series, in approximately 20% of the cases it was not easy to discriminate between BDC and CCC. Hepatobiliary surgeons and pathologists should be aware of the differences between BDC and CCC. In addition, the examination of a greater number of cases and the use of immunohistological or genetic techniques may provide a better understanding of these two conditions.[22]

With respect to the surgical procedures, HPD[20] to secure the distal bile duct margin was done significantly more frequently in BDC patients. This difference implies that, among the BDC cases, there was extensive longitudinal extension along the extrahepatic bile duct, which may account for the significantly higher cancer-positive rates of the proximal and distal bile duct margins among the BDC patients. The rate of portal vein resection and reconstruction was comparable in the BDC and CCC patients. In our protocol, the decision to perform a right- or left-sided hepatectomy is made based on the predominant location of the tumor. When the tumor involved the right and left or proximal bile duct equally, right-sided hepatectomy was the first choice; this situation commonly occurs in BDC patients. Thus, a right-sided hepatectomy and prior PVE were performed significantly more frequently in BDC patients.

The bile duct margins must be clear of cancer to achieve cure; many previous reports have suggested that the presence of clear margins is an independent prognostic factor,[3–6,10–13,21] which is consistent with the results seen in our CCC patients. In BDC patients, the proportion of positive proximal bile duct margin was 29%, and R0 resection was achieved in 59%. This figure is lower than the 70% or greater cancer-negative surgical margins previously reported in large series.[3,5,7,9,12,13,23] The relatively high rate of cancer-positive surgical margins in the present study may be attributed to the strict diagnostic criteria used for bile duct margins or due to institutional differences in the diagnostic criteria. Nevertheless, the overall 5-year survival rate of 38.4% for BDC patients in our series is at least comparable to previous reports.[3,5,7,9,12,13,23] Further research is needed to clarify the diagnostic accuracy of bile duct margins[24,25] and the impact of positive bile duct margins on survival.[26,27]

Although the rates of red blood cell (RBC) transfusion requirement in both CCC and BDC group were comparable, CCC patients who underwent RBC transfusion showed a significantly shorter survival than those who did not undergo transfusion. On the other hand, there was no significant survival difference in BDC patients in terms of RBC transfusion. In patients with hepatocellular carcinoma (HCC), Yamamoto et al.[28] pointed out that perioperative RBC transfusion promotes tumor recurrence after hepatectomy. This may support that CCC, classified into primary liver tumor as same as HCC, potentially has a different character from BDC classified into bile duct tumor.

In summary, the overall survival of BDC patients was significantly better than that of CCC patients. On univariate analysis, only a few of the statistically significant clinicopathological factors were the same in the two groups; on multivariate analysis, there were no common significant predictive factors. Thus, BDC and CCC appear to show different biological behaviors. Differentiating between these two conditions would have an impact on the ability to predict postoperative survival.

## ACKNOWLEDGMENT

This research was supported in part by a Grant-in-Aid for scientific research from the Ministry of Health and Welfare of Japan.

## REFERENCES

1. Nimura Y, Hayakawa N, Kamiya J, Kondo S, Shionoya S. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg* 1990; 14:535–43.
2. Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. *Arch Surg* 1995; 130:270–6.
3. Klempnauer J, Ridder GJ, von Wasielewski R, Werner M, Weiman A, Pichlmayr R. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. *J Clin Oncol* 1997; 15:947–54.
4. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999; 230:808–18.
5. Miyazaki M, Ito H, Nakagawa K, et al. Parenchyma-preserving hepatectomy in the surgical treatment of hilar cholangiocarcinoma. *J Am Coll Surg* 1999; 189:575–83.
6. Kosuge T, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg* 1999; 230:663–71.
7. Nimura Y, Kamiya J, Kondo S, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg* 2000; 7:155–62.
8. Gerhards MF, van Gulik TM, de Wit LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma: a single center experience. *Surgery* 2000; 127:395–404.
9. Lee SG, Lee YJ, Park KM, Hwang S, Min PC. One hundred and eleven liver resections for hilar bile duct cancer. *J Hepatobiliary Pancreat Surg* 2000; 7:135–41.
10. Seyama Y, Kubota K, Sano K, et al. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. *Ann Surg* 2003; 238:73–83.
11. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. *Ann Surg* 2003; 238:84–92.
12. Hemming AW, Reed AI, Fujita S, Foley DP, Howard RJ. Surgical management of hilar cholangiocarcinoma. *Ann Surg* 2005; 241:693–702.
13. Jarnagin WR, Bowne W, Klimstra DS, et al. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. *Ann Surg* 2005; 241:703–14.
14. Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resection for perihilar cholangiocarcinoma with zero mortality. *Ann Surg* 2006; 244:240–7.
15. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990; 107:521–7.
16. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 2006; 243:364–72.
17. Sano T, Kamiya J, Nagino M, et al. Macroscopic classification and preoperative diagnosis of intrahepatic cholangiocarcinoma in Japan. *J Hepatobiliary Pancreat Surg* 1999; 6:101–7.
18. In: Sobin LH, Wittekind C (eds). International Union Against Cancer (UICC): TNM Classification of Malignant Tumors 6th ed. New York: Wiley-Liss; 2002.
19. Cox D, Oakes D. Analysis of Survival Date London: Chapman and Hall; 1983.
20. Nimura Y, Hayakawa N, Kamiya J, et al. Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. *Hepatogastroenterolog* 1991; 38:170–5.
21. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996; 224:463–73.
22. Jarnagin WR, Klimstra DS, Hezel M, et al. Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. *J Clin Oncol* 2006; 24:1152–60.
23. Kondo S, Hirano S, Ambo Y, et al. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. *Ann Surg* 2004; 240:95–101.
24. Sakamoto E, Nimura Y, Hayakawa N, et al. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg* 1998; 227:405–11.
25. Ebata T, Watanabe H, Ajioka Y, Oda K, Nimura Y. Pathological appraisal of lines of resection for bile duct carcinoma. *Br J Surg* 2002; 89:1260–7.
26. Wakai T, Shirai Y, Moroda T, Yokoyama N, Hatakeyama K. Impact of ductal resection margin status on long-term survival in patients undergoing resection for extrahepatic cholangiocarcinoma. *Cancer* 2004; 103:1210–6.
27. Sakamoto Y, Kosuge T, Shimada K, et al. Prognostic factors of surgical resection in middle and distal bile duct cancer: an analysis of 55 patients concerning the significance of ductal and excisional margins. *Surgery* 2005; 137:396–402.
28. Yamamoto J, Kosuge T, Takayama T, et al. Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. *Surgery* 1994; 115:303–9.

# Minimally Invasive Intraductal Papillary-mucinous Carcinoma of the Pancreas: Clinicopathologic Study of 104 Intraductal Papillary-mucinous Neoplasms

*Satoshi Nara, MD,* Kazuaki Shimada, MD, PhD,† Tomoo Kosuge, MD, PhD,† Yae Kanai, MD, PhD,* and Nobuyoshi Hiraoka, MD, PhD**

**Abstract:** Invasive intraductal papillary-mucinous carcinoma (I-IPMC) is a heterogeneous entity with various postoperative outcomes. The aim of this study is to characterize early-stage I-IPMC with nonaggressive characteristics. One hundred and four patients with intraductal papillary-mucinous neoplasm (IPMN) were clinicopathologically investigated. The lesions were classified into 53 noninvasive IPMNs (adenoma, borderline, and noninvasive IPMC) and 51 I-IPMCs on the basis of the WHO classification. I-IPMCs were divided further into 26 minimally invasive IPMCs (MI-IPMCs) and 25 invasive carcinomas originating in IPMC (IC-IPMCs) by new diagnostic criteria proposed in this study. We examined invasiveness of I-IPMC on 4 patterns, and defined simple and practical diagnostic criteria of minimal invasion for each invasive pattern. The disease-specific survival rates after 3, 5, and 10 years were 100%, 100%, and 100% for both noninvasive IPMN and MI-IPMC, and 51%, 38%, and 0% for IC-IPMC. The overall and disease-specific survival rates for MI-IPMC were both significantly better than those for IC-IPMC ($P < 0.001$), but there was no significant difference between noninvasive IPMN and MI-IPMC. Multivariate analysis showed that the factors indicative of poor prognosis were a diagnosis of I-IPMC classified as IC-IPMC and a high level of serum carbohydrate antigen 19-9. The prognosis of IC-IPMC was not significantly different from that of pancreatic ductal carcinoma in each of the corresponding tumor-node-metastasis stages. These findings suggest that a category of MI-IPMC provides more accurate and useful information of the stage and the aggressiveness of I-IPMC.

**Key Words:** intraductal papillary-mucinous neoplasms of the pancreas, minimal invasion, prognosis, clinicopathologic analysis, invasive pattern

(*Am J Surg Pathol* 2008;32:243–255)

From the *Pathology Division, National Cancer Center Research Institute; and †Division of Hepato-Biliary and Pancreatic Surgery, National Cancer Center Hospital, Tokyo.

Supported by a Grant-in-Aid for Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors have no direct or indirect commercial and financial incentive associated with publishing the article.

Reprints: Nobuyoshi Hiraoka, MD, PhD, Pathology Division, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: nhiraoka@gan2.res.ncc.go.jp).



Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas is a well-characterized clinical and pathologic entity. IPMNs are characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae and lead to cystic dilation of the pancreatic ducts, forming clinically and macroscopically detectable masses.[15] Similarly to the well-defined adenoma-carcinoma sequence in colorectal cancer,[5] IPMNs progress from intraductal papillary-mucinous adenoma (IPMA) to borderline IPMN, then to intraductal papillary-mucinous carcinoma (IPMC), and eventually to invasive adenocarcinoma.[2,9,10] According to the WHO classification,[13,15] IPMC is classified as either "noninvasive" or "invasive." It is reported that noninvasive IPMN shows a favorable postoperative outcome in comparison with invasive IPMC (I-IPMC), with 5-year survival rates ranging from 77% to 100%.[4,6,16,20,22,24] With regard to the prognosis of I-IPMC, there is a substantial variation in the 5-year survival rates from 24% to 60% in previous reports.[4,6,16,20,22–24] This may be due to heterogeneity of I-IPMCs, including an invasive component of various sizes and biologic behavior. Our hypothesis is that the prognosis of I-IPMC can be substantially determined by the degree and type of invasion, and thus I-IPMC can be classified as either aggressive or nonaggressive by categorization according to the extent and pattern of invasion. Such a classification would be clinically relevant for deciding whether surgery is indicated, for selecting the most appropriate surgical procedure, and for prediction of postoperative outcome.

The concept of minimally invasive cancer was originally introduced for uterine cervical cancer showing very early invasion and a favorable prognosis.[26] Minimally invasive IPMC (MI-IPMC) has been categorized within the classification of pancreatic carcinoma used by the Japan Pancreatic Society (JPS) since 1993.[12] In the JPS classification, I-IPMC is classified into 2 categories: MI-IPMC and invasive carcinoma originating in IPMC (IC-IPMC), the latter being more advanced. A few reports have indicated that MI-IPMC has a better surgical outcome than IC-IPMC.[19,25,27] However, the definition of "minimal invasion" has not been clear. In the original JPS text, it is described only as "slight invasion beyond the pancreatic duct wall."[12]

In this retrospective study, we evaluated the invasiveness of I-IPMC by the examination of 4 invasive

patterns, and tried to define simple and practical diagnostic criteria of minimal invasion for each invasive pattern. The clinical relevance of this subdivision was then evaluated in terms of postoperative survival.

## MATERIALS AND METHODS

### Study Population

This study was approved by the Ethics Committee of the National Cancer Center, Japan. Between January 1984 and December 2005, 111 patients underwent pancreatic resection for IPMNs at the National Cancer Center Hospital, Japan. There were no operation-related deaths, and all patients underwent macroscopically curative resection without any residual tumor. Seven cases also had ductal carcinoma of the pancreas, which was not directly associated with IPMNs. Excluding these patients, 104 cases of IPMN were included in this study. The patients comprised of 56 males and 48 females with a median age of 66 (41 to 84) years. The operative procedures included 12 pancreatoduodenectomies (PDs), 59 pylorus-preserving PDs (PPPDs), 24 distal pancreatectomies, 3 total pancreatectomies, 5 partial pancreatectomies, and 1 PPPD with distal pancreatectomy. These procedures accounted for 18.9% of all pancreatectomies (n = 551) performed at our institution for pancreatic tumors during the same period.

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 dropped out during follow-up. Clinical or radiologic data and follow-up information for every patient were obtained from the medical records. The median follow-up period after surgery was 37.2 (4.2 to 210) months for all patients, 52.9 (4.2 to 171) months for noninvasive IPMN, 43.4 (13.2 to 210) months for MI-IPMC, and 20.4 (7.1 to 87.7) months for IC-IPMC.

### Pathologic 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 pancreas body and tail. All the sections were stained with hematoxylin and eosin for pathologic examination. If necessary, additional staining for elastic fibers (elastica stain) was performed. After histopathologic examination of all the sections, the lesion was classified as IPMA, borderline IPMN, noninvasive IPMC, or I-IPMC according to the WHO classification.[13,15] The lesion was graded by the highest degree of atypia. I-IPMCs were divided further into MI-IPMC or IC-IPMC according to our proposed criteria (Table 1) described later. We evaluated the invasiveness of I-IPMC, and the 4 invasive patterns were examined: "infiltrative growth," "mucous rupture," "expansive growth," and "intra-abdominal rupture." The criterion of minimal invasion was proposed for each invasive pattern. I-IPMC showing some features of minimal invasion without any features categorized in IC-IPMC was classified as MI-IPMC. I-IPMC showing at least one invasive feature beyond minimal invasion is classified as IC-IPMC. For example, if an I-IPMC shows mucous rupture and infiltrative growth of tubular adenocarcinoma with 6-mm length of invasion, this tumor is diagnosed as IC-IPMC.

An infiltrative growth pattern, which is commonly found in conventional invasive ductal carcinoma of the pancreas, is considerably aggressive (Figs. 1A–D). Among the 6 patients with IC-IPMC, in whom the depth of infiltration of carcinoma cells ranged from 6 to 20 mm, 3 patients (including a patient with 6-mm-length infiltration of carcinoma cells) had recurrence in the liver or peritoneal cavity, and died of the disease. This suggests that infiltrative growth is strongly associated with a high rate of recurrence and mortality, even if the size of invasion is limited. On the other hand, none of the 17 patients with a maximum infiltration of 5 mm or less had recurrence except 2 patients, 1 of them had 2-mm-length infiltration of tubular adenocarcinoma and the other had 2-mm-length infiltration of pure mucinous carcinoma. Therefore, we adopted a threshold of 5 mm as a diagnostic criterion for minimal invasion in infiltrative growth (Table 1). Lymphatic, venous, and neural invasion are treated as a part of infiltration of cancer cells. Invasion of 5 mm or less is sometimes difficult to detect. In such cases, elastica staining was helpful for differentiating infiltrating carcinoma from intraductal spreading of carcinoma (Figs. 1C, D).

IPMN is characterized by its prominent mucus secretion into the lumen, in some cases, into the space between epithelial cells and basement membrane due to inverted cellular polarity, which subsequently causes disruption of the pancreatic duct wall and spilling of mucus into the interstitial space.[1,7] This is referred to mucous rupture (Fig. 2) and is diagnosed as minimal invasion if mucous lakes are not associated with mucinous carcinoma showing infiltrative growth (Table 1). Mucous rupture was observed only in the vicinity of the pancreatic ductal system, although the location was not confined to the pancreas. We considered mucus lakes near noninvasive IPMC as mucous rupture regardless of the presence of viable cancer cells within it, because viable cancer cells may be present floating in the mucus lake. When viable cancer cells floating in mucus lake are apparently present and are scant (there is very small number of cancer cells or their clusters floating in only the limited mucus lakes. The representative feature was shown in Fig. 2D), this situation is called as "mucous rupture with cellular component." This subcategory includes a kind of pure mucinous carcinoma (alternatively colloid carcinoma)[1] showing a very low cellularity, and nonmucinous cancer cells which are simply detached from the duct wall and are floating in mucus lake. Mucous rupture without floating cancer cells represented the suspected lesion of mucous rupture with cellular component. When there are many cancer cells (more than "scant" level) floating in mucus lake, it is judged as infiltrative growth of mucinous carcinoma (Figs. 2E, F).

**TABLE 1.** Growth Patterns of I-IPMCs and Diagnostic Criteria for Minimal Invasion

| Growth Pattern | Pathologic Features | Minimal Invasion | Beyond Minimal Invasion (IC-IPMC) |
|---|---|---|---|
| Infiltrative growth | Carcinoma cells from the pancreatic duct occupied by IPMC invade the surrounding stroma. Disappearance of the basement membrane or desmoplastic change around the ducts implies interstitial invasion. Infiltrative distance is defined as the length from the deepest point of invasion to the stroma surface of the nearest non-invasive IPMC | 1. An infiltrative distance of 5 mm or less is regarded as minimal invasion<br>2. Venous, lymphatic, or neural invasion within the area (≤5 mm of the infiltrative distance) is also counted in this category<br>3. This category includes the invasion of various histologic types of cancer, such as tubular adenocarcinoma, mucinous carcinoma, etc | 1. An infiltrative distance more than 5 mm is regarded as IC-IPMC<br>2. Venous, lymphatic, or neural invasion within the area ( > 5 mm of the infiltrative distance) is also counted in this category<br>3. This category includes the invasion of various histologic types of cancer, such as tubular adenocarcinoma, mucinous carcinoma, etc |
| Mucous rupture | "Mucous rupture" and "expansive growth" are unique features of IPMC that grows intraductally and secretes large amounts of mucus. The mucus spills out, forming a mucus lake around the pancreatic duct, due to rupture of the dilatated pancreatic duct occupied by IPMN through high pressure caused by the hypersecreted mucin. This is referred to mucous rupture. Mucous lakes of various sizes are seen, sometimes containing scanty floating cancer cells | 1. If mucous lakes are not associated with mucinous carcinoma showing infiltrative growth, this feature is diagnosed as minimal invasion, regardless of the size and location of the mucus lakes<br>2. If a mucus lake contains scanty floating cancer cells (there is very small number of cancer cells or their clusters floating in only the limited mucus lakes. The representative feature was shown in Fig. 2D), it is additionally described as "mucous rupture with cellular component." This subcategory includes a kind of pure mucinous carcinoma associated with IPMC<br>3. If many cancer cells (more than "scant" level) are floating in mucus lakes (Fig. 2E), it is treated as "infiltrative growth" of mucinous carcinoma and the infiltrative distance of 5 mm or less is regarded as minimal invasion | 1. If many cancer cells are floating in mucus lakes, it is treated as "infiltrative growth" of mucinous carcinoma and the infiltrative distance of more than 5 mm is classified as IC-IPMC |
| Expansive growth | A pancreatic duct is markedly dilated, becoming ductectatic or cystic in shape. The basement membrane and subepithelial elastic fibers may be elongated and disrupted. Cystic IPMC may grow expansively into peripancreatic connective tissues, and eventually involves the bowel or major vessels [portal vein (PV), SPV, SMV, or splenic artery (SPA)] | 1. Loss of the basement membrane of the pancreatic duct with IPMC is regarded as minimal invasion<br>2. If I-IPMC grows expansively, even if it ruptures into the bowel, or even if it erodes a major vessel wall unless cancer cells enter the lumen of the major vessel, it is still regarded as minimal invasion<br>3. If I-IPMC has this type of growth as predominance, it is corresponded to a kind of pure mucinous carcinoma associated with IPMC | 1. If I-IPMC forms a fistula with a major vessel, it is regarded as IC-IPMC |
| Intra-abdominal rupture | IPMC ruptures into the abdominal cavity, and mucus-secreting cancer cells are scattered in it | Peritoneal dissemination may occur. Therefore, this finding should be distinguished from ordinary IPMN and classified separately as ruptured IPMN. MI- or IC-IPMC should be noted additionally | |
| Judgement | | An I-IPMC showing some features of minimal invasion without any features categorized in IC-IPMC is classified as MI-IPMC | An I-IPMC showing at least one invasive feature beyond minimal invasion is classified as IC-IPMC |

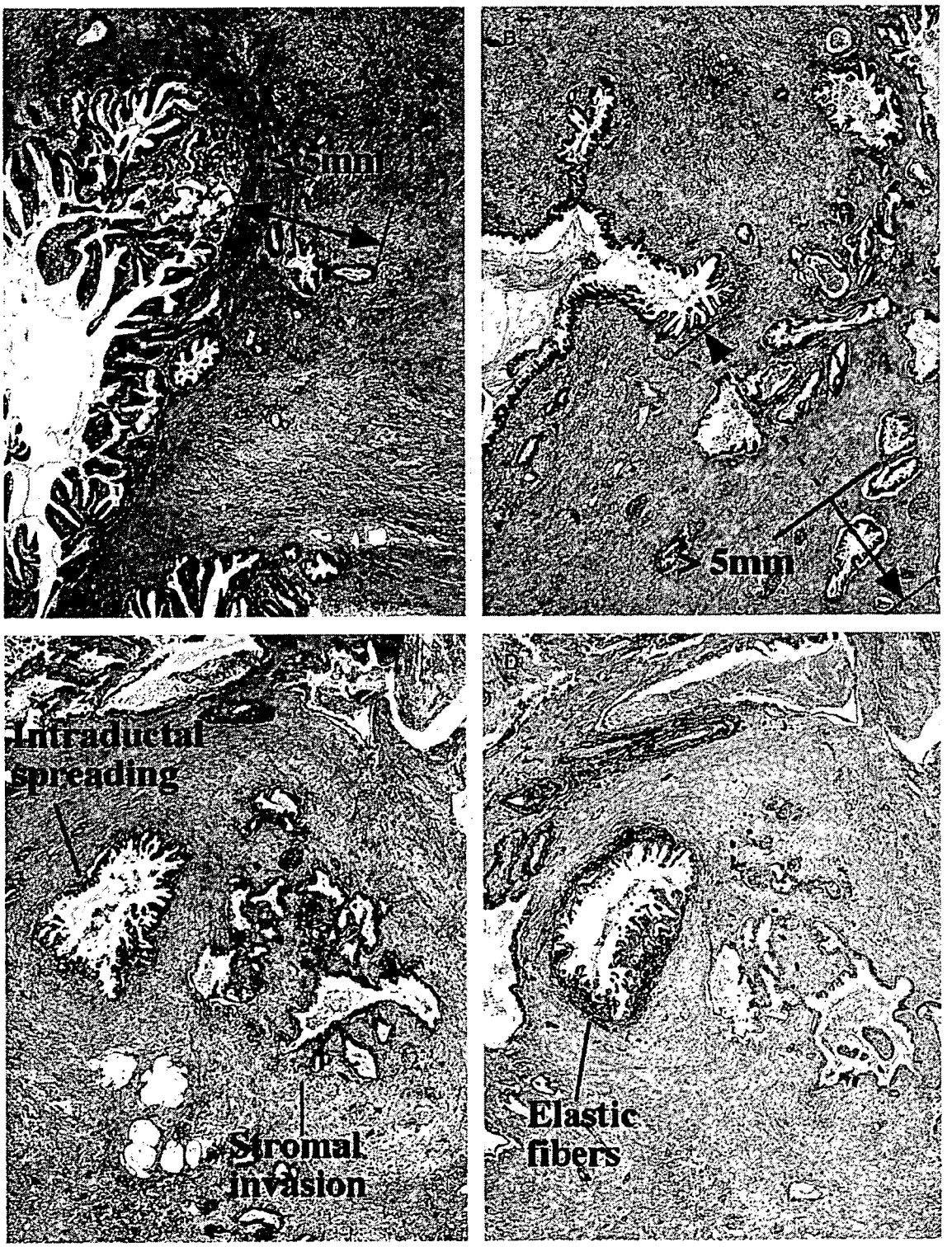



**FIGURE 1.** Histopathologic features of "infiltrative growth" in I-IPMC. A and B, Histologic features resemble those of conventional invasive ductal carcinoma of the pancreas. The arrows indicate the depth of infiltration of invasive carcinoma. If the depth is less than 5 mm, it is regarded as minimal invasion (A), and if the depth is more than 5 mm it is regarded as IC-IPMC (B). C and D, Elastica stain (D) helps to discriminate infiltrative growth from intraductal spread of carcinoma. The former lacks a positively stained sheath of elastic fibers (black) around the pancreatic duct. Hematoxylin and eosin stain (C).

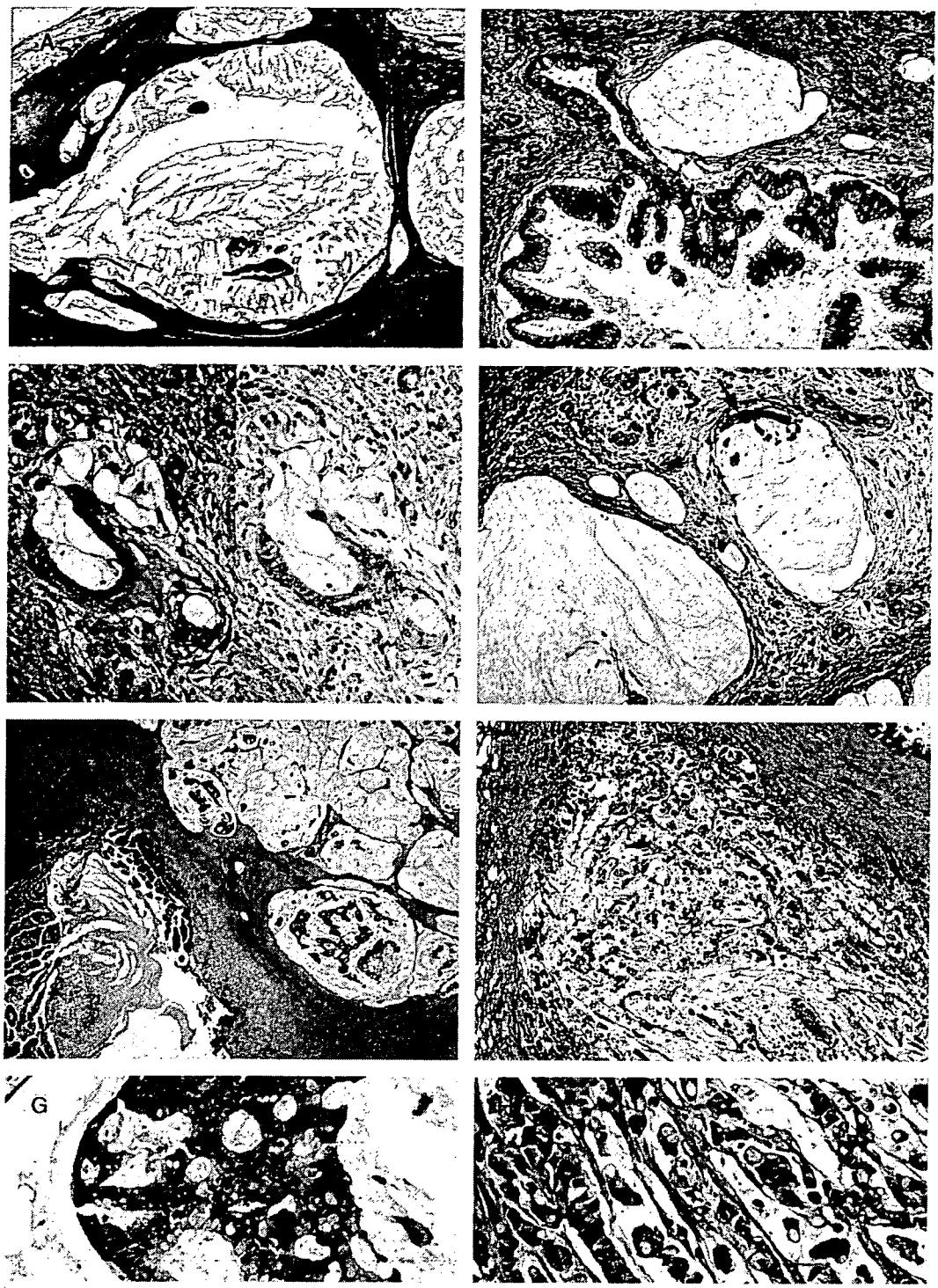



**FIGURE 2.** Histopathologic features of "mucous rupture" and "infiltrative growth" of mucinous carcinoma in I-IPMC. A to D, "Mucous rupture" pattern. Part of the pancreatic duct is disrupted and mucus leakage is evident. Variable sizes of mucus lakes without viable cancer cells floating are observed (A–C). A small duct covered by elastic fibers (C right column; elastica stain) is broken and the mucus leaks to form mucus lake (C). A small number of cancer cells (arrow) are floating in mucus lakes, which is described as "mucous rupture with cellular component." We could not observe any floating cancer cells in mucus lakes other than this cluster of cancer cells (arrow) in the entire lesion of the I-IPMC (D). E to H, "Infiltrative growth" of mucinous carcinoma. Many cancer cells floating in mucus lakes (E, G) or infiltrating features of mucinous carcinoma (F, H) are categorized as "infiltrative growth" of mucinous carcinoma. G and H, High-power view of (E) and (F), respectively.

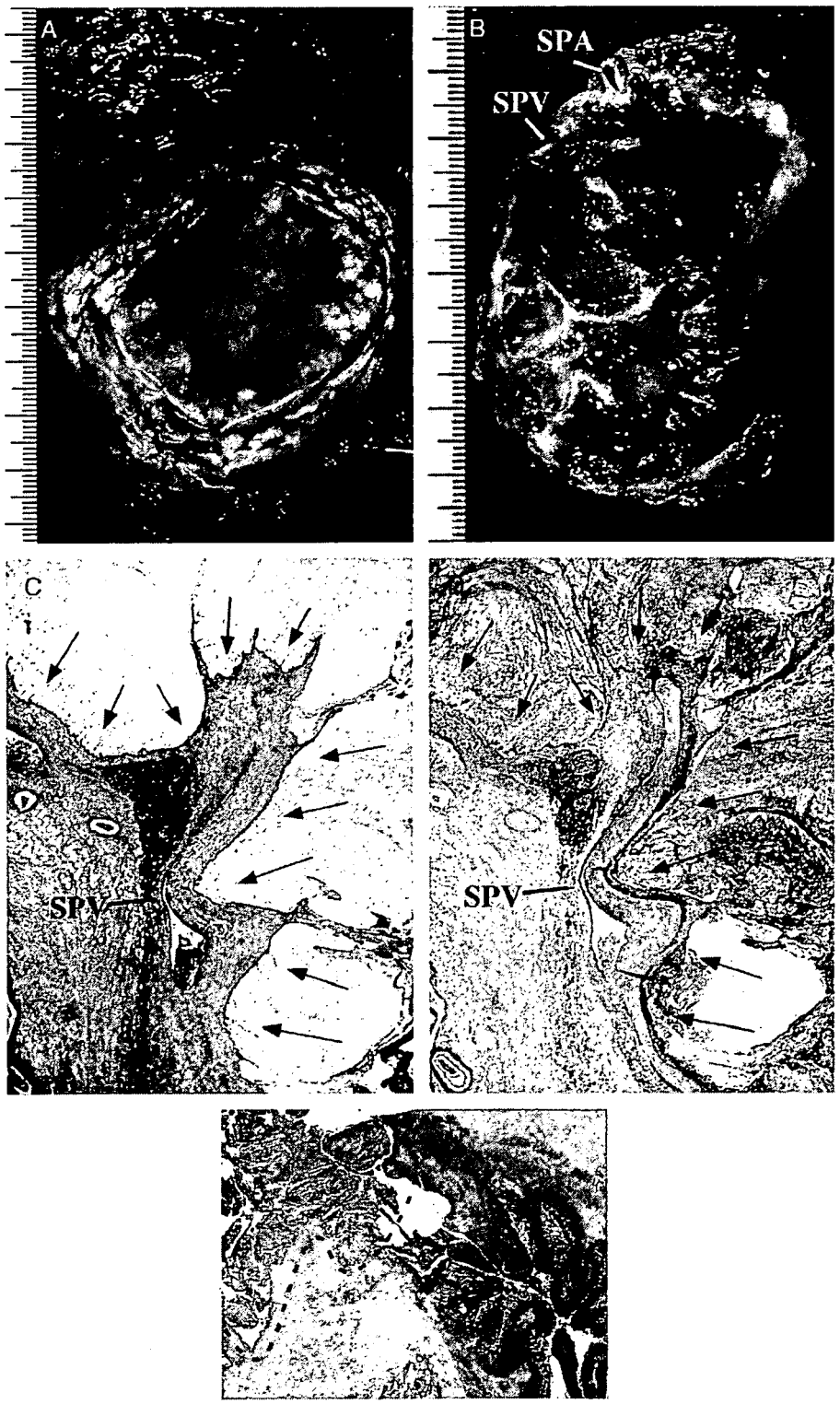



**FIGURE 3.** Histopathologic features of "expansive growth" in I-IPMC. The pancreatic duct is markedly dilated to a cystlike shape (A, B). Fresh cut view (A) and formalin-fixed cut surface (B) of cystic I-IPMCs. Cystically dilated pancreatic duct is filled with clear mucus and many papillary projections are seen on the inner surface (A). The SPV is compressed (B–D) and its thickened wall is eroded by an enlarged cystic IPMC (arrows) in hematoxylin and eosin stain (C) and elastica stain (D). A fistula has been formed between cystic I-IPMC (dotted line) and duodenum (E).

All of the 24 patients with mucous rupture MI-IPMC survived after surgery.

Expansive growth of ductectatic or cystic IPMN is another characteristic feature of IPMN (Fig. 3). In addition to mucous rupture, an increase of intraductal pressure by hypersecretion of mucus causes marked cystic dilatation of the duct, which continues to grow expansively into extrapancreatic tissue. In some cases, cystic IPMC eventually forms a fistula with surrounding digestive organs (Fig. 3E) or erodes the wall of major blood vessels [portal vein, splenic vein (SPV), superior mesenteric vein (SMV), or splenic artery] (Figs. 3C–E). Such growth and spread are rather passive in contrast to the infiltrative growth that occurs in active invasion and this feature was not associated with poor prognosis, similarly to mucous rupture. IPMC showing expansive growth with loss of the basement membrane of the pancreatic duct in the IPMC is diagnosed as MI-IPMC. If I-IPMC grows expansively, even if it ruptures into the bowel, or even if it erodes a major vessel wall unless cancer cells enter the lumen of the major vessel, it is still regarded as minimal invasion (Table 1). If I-IPMC has this type of growth as predominance, it is corresponded to a kind of pure mucinous carcinoma associated with IPMC.

Although we have not yet experienced intra-abdominal rupture of IPMC, a few cases have been reported.[18] As intra-abdominal rupture was followed by peritoneal dissemination in these reported cases, this type should be distinguished from ordinary IPMN and managed separately as ruptured IPMN.

IC-IPMC was defined as a lesion consisting of IPMN and invasive carcinoma with the predominance of the IPMN component.[12] Such invasive carcinoma exceeds the minimal invasion proposed in Table 1, and shows a continuous transition between invasive carcinoma and intraductal IPMC. In this study, we added new group of cases to the original IC-IPMC category, which had invasive carcinoma apparently originated from IPMN but predominant over the IPMN component. We wanted to compare the prognosis between IC-IPMC and conventional invasive ductal carcinoma of the pancreas in the matched tumor-node-metastasis (TNM) stages.[11]

### Statistical Analysis

Comparisons of qualitative variables were performed using the $\chi^2$ test or Fisher exact test. One-way analysis of variance was used to compare the means of 3 or more groups. The postoperative overall and disease-specific survival rates were calculated by the Kaplan-Meier method. Univariate analysis was performed for prognostic factors using the log-rank test. The factors found to be predictive by univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model. Differences at $P < 0.05$ were considered statistically significant. Statistical analyses were performed with SPSS 11.0J software (SPSS Inc, Chicago, IL).

## RESULTS

### Histopathologic Evaluation of I-IPMC

One hundred and four IPMNs were classified into 27 IPMAs, 11 borderline IPMNs, 15 noninvasive IPMCs, and 51 I-IPMCs according to the WHO classification.[13,15] None of them had an ovarianlike stroma, and all the lesions showed communication with the pancreatic ductal system. I-IPMCs were further divided into 26 MI-IPMCs and 25 IC-IPMCs according to our criteria (Table 1) based on the histopathologic pattern of invasion.

To evaluate the aggressive characteristics of I-IPMC, we examined the invasiveness of I-IPMC. The invasiveness was categorized into 4 patterns: infiltrative growth, mucous rupture, expansive growth, and intra-abdominal rupture (see Materials and Methods). The criterion of minimal invasion was proposed for each corresponding pattern (Table 1), and the representative features are shown in Figures 1 to 3.

Seventeen among 26 patients with MI-IPMC showed infiltrative growth pattern (Fig. 1). Histologic types of the infiltrating cancer cells were tubular adenocarcinoma in 7 patients, mixed tubular adenocarcinoma and mucinous carcinoma in 2 patients, pure mucinous carcinoma in 5 patients, and papillary adenocarcinoma in 3 patients. The average depth of infiltration was 1.5 mm (range from < 1 to 5 mm). None of the 17 patients with a maximum infiltration of 5 mm or less had recurrence with exception of 2 patients, one of them had 2-mm-length infiltration of tubular adenocarcinoma and the other had 2-mm-length infiltration of pure mucinous carcinoma.

The most of the patients with MI-IPMC had mucous rupture and 6 patients had MI-IPMC with mucous rupture as predominant invasive pattern (Fig. 2). Two of them were subcategorized as mucous rupture with cellular component. None of these 6 patients had recurrence.

Expansive growth (Fig. 3) was often observed in cystically growing tumors and 4 patients with MI-IPMC mentioned below showed expansive growth as predominance. In 2 patients with I-IPMC, a fistula was formed between the IPMN and the duodenum. No cancer cells infiltrating the duodenal wall were detected in either case by histologic examination (Fig. 3E). It was suspected that the fistulas were formed by rupture of the expansively growing IPMN into the adjacent duodenum. The lesion was classified as MI-IPMC (expansive growth) in 1 patient, but the other patient had definite invasive cancer in the pancreas tail distant from the fistula, and was therefore diagnosed as having IC-IPMC. Whereas the former patient had no recurrence 107 months after surgery, the latter patient developed local lymph node (LN) metastasis 6 months after surgery and died of the disease. In the other 3 patients with expansive growth of MI-IPMC, the IPMN had grown deeply into the retropancreatic tissue, compressing the wall of the SPV or SMV. In one of them, the tunica media of the SPV was involved without a fistula

**TABLE 2.** Comparison of Invasive Lesion Between MI-IPMC and IC-IPMC

| | MI-IPMC (n = 26) | IC-IPMC (n = 25) | P* |
|---|---|---|---|
| Growth pattern | | | |
| Infiltrative growth | 17 | 25 | |
| Mucous rupture or expansive growth as predominance | 10† | 0 | |
| Vessel or neural invasion | 4 | 25 | **< 0.001** |
| Lymphatic invasion | 0 | 23 | **< 0.001** |
| Venous invasion | 2 | 24 | **< 0.001** |
| Intrapancreatic neural invasion | 2 | 22 | **< 0.001** |
| Extrapancreatic involvement | 4 | 23 | **< 0.001** |
| Serosa | 0 | 4 | 0.051 |
| Retropancreatic tissue | 3‡ | 21 | **< 0.001** |
| Duodenum | 1‡ | 8 | **0.002** |
| Extrahepatic bile duct | 0 | 3 | 0.110 |
| Portal venous system | 1‡ | 8 | **0.011** |
| Arterial system | 0 | 1 | 0.490 |
| Extrapancreatic nerve plexus | 0 | 4 | 0.051 |
| Invasion to surgical margin | 0 | 4 | 0.051 |
| Metastasis | 0 | 17 | **< 0.001** |
| Local LN | 0 | 17 | **< 0.001** |
| Distant organs | 0 | 4§ | 0.051 |
| TNM stage | | | **< 0.001** |
| IA | 22 | 1 | |
| IB | 0 | 0 | |
| IIA | 4 | 7 | |
| IIB | 0 | 13 | |
| III | 0 | 0 | |
| IV | 0 | 4§ | |
| Histology of infiltrative growth | | | |
| Pap | 3 | 2 | |
| Tub1 | 7 | 5 | |
| Tub2 | 0 | 8 | |
| Tub + Muc | 2 | 7 | |
| Tub3 | 0 | 1 | |
| Muc | 5 | 1 | |
| AS | 0 | 1 | |

Statistically significant value is in bold characters.

*$P$ value was calculated by $\chi^2$ or Fisher exact test.

†6 patients showed mucous rupture (2 of them showed mucous rupture with cellular component) and 4 patients showed expansive growth (one of them showed infiltrative growth as well).

‡Due to expansive growth.

§One patient with liver metastasis, 3 patients with para-aortic LN metastasis.

AS indicates adenosquamous carcinoma; Muc, mucinous carcinoma; Pap, papillary adenocarcinoma; Tub1, well-differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma; Tub3, poorly differentiated tubular adenocarcinoma.

between tumor and SPV (Figs. 3C–E). These 3 patients did not have postoperative recurrence at 28, 52, and 96 months after surgery, respectively. We thought mucous rupture and expansive growth is dormant invasion, considering its nonaggressive nature, which is characteristic to IPMN.

Comparison of the pathologic characteristics and TNM staging[11] between invasive lesions of MI-IPMCs and IC-IPMCs are summarized in Table 2. Vessel or neural invasion and extrapancreatic involvement were much more common in IC-IPMC than in MI-IPMC. No LN metastasis was observed in patients with MI-IPMC, whereas 17 patients (68%) with IC-IPMC showed LN metastasis. With regard to the histology of the invasive component of the IC-IPMC, most of the patients had tubular adenocarcinoma and only 1 patient had pure mucinous carcinoma. Among 26 patients with MI-IPMC, 9 had tubular adenocarcinoma and 11 had pure mucinous carcinoma.

## Prognostic Significance of the Classification of I-IPMC

The median survival period for the 104 patients was 142 months, and the 3, 5, and 10-year overall survival rates were 86%, 78%, and 59%, respectively. There was no statistically significant difference in overall survival among patients with IPMA, borderline IPMN, and noninvasive IPMC ($P = 0.54$). Therefore, they were integrated into noninvasive IPMN for subsequent analysis. The survival rates 3, 5, and 10 years after surgery were 95%, 92%, and 70% for noninvasive IPMN, 95%, 79%, and 79% for MI-IPMC, and 51%, 38%, and 0% for IC-IPMC (Fig. 4A). The disease-specific survival rates after 3, 5, and 10 years were 100%, 100%, and 100% for noninvasive IPMN, 100%, 100%, and 100% for MI-IPMC, and 51%, 38%, and 0% for IC-IPMC (Fig. 4B). Overall and disease-specific survival for MI-IPMC was significantly better than for IC-IPMC ($P < 0.001$), whereas there was no significant difference in overall survival between noninvasive IPMN and MI-IPMC ($P = 0.66$).

Overall survival was compared between I-IPMC and conventional invasive ductal carcinoma of the pancreas during the same period (Figs. 5A–D). The stages of IC-IPMCs were assessed on the basis of size and spread of invasive carcinoma in the lesion, using the International Union against Cancer (UICC) TNM classification,[11] and classified as stage IA, IB, and IIA, stage IIB, and stage III and IV. Between IC-IPMC and conventional invasive ductal carcinoma of the pancreas at each corresponding TNM stage, there was no statistically significant difference in survival rate, though IC-IPMC had a tendency to show a favorable outcome.

## Prognostic Factors in I-IPMCs

Clinicopathologic factors possibly affecting the postoperative outcome of I-IPMCs were studied (Table 3). The following variables were significantly related to unfavorable prognosis: presence of jaundice, cancer cells present at the surgical margin except the pancreatic margin, presence of major vascular invasion [portal vein, SMV, SPV, or splenic artery], presence of lymphatic invasion, presence of venous invasion, presence of intrapancreatic neural invasion, presence of LN metastasis, presence of para-aortic LN metastasis, CA19-9 > 300 U/mL, size of invasive cancer > 2 cm, histopathologic diagnosis of IC-IPMC (vs. MI-IPMC), and tubular adenocarcinoma as histologic type of invasive cancer in I-IPMC. Multivariate analysis (backward elimination method) showed that a histopathologic diagnosis of I-IPMC classified as IC-IPMC and

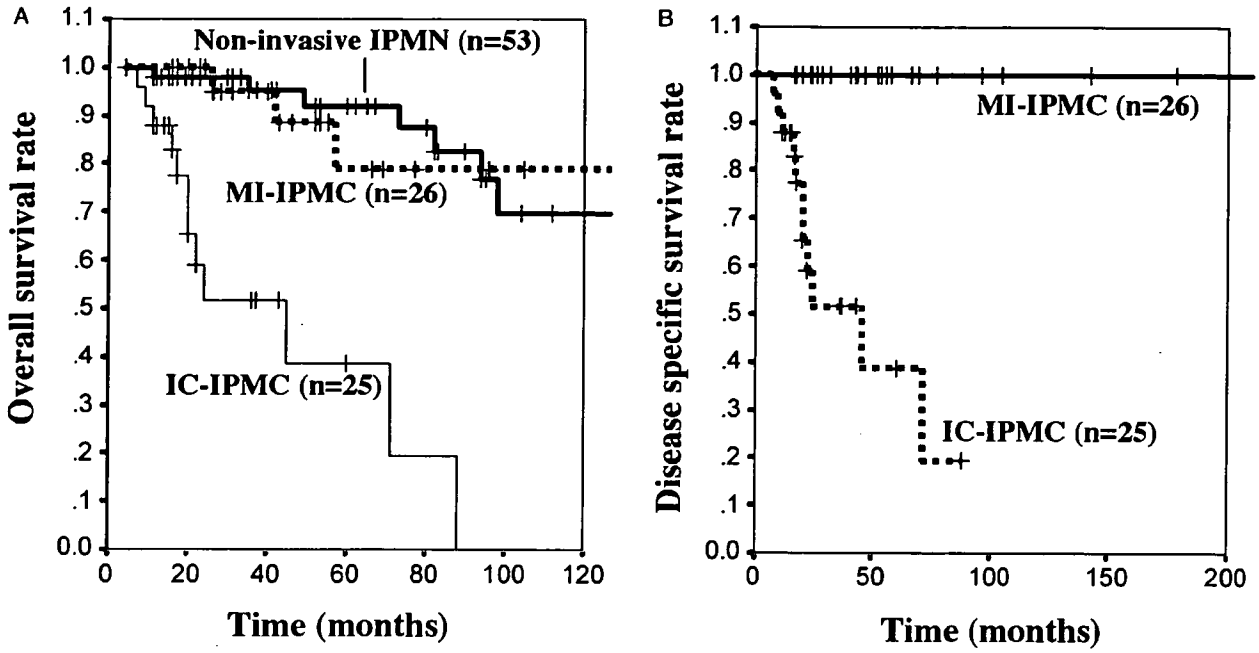



**FIGURE 4.** Kaplan-Meier survival curves of the 104 patients with IPMNs. A, Overall survival of patients with MI-IPMC was significantly better than that of patients with IC-IPMC ($P<0.001$), whereas no significant difference was found between patients with noninvasive IPMN and those with MI-IPMC ($P=0.66$). B, Disease-specific survival of patients with MI-IPMC was significantly better than that of patients with IC-IPMC ($P<0.001$), with no disease-related death among 26 patients with MI-IPMC during a median follow-up period of 43.4 (13.2 to 210) months.

CA19-9 > 300 U/mL were significant prognostic factors (Table 4).

## Postoperative Recurrence of IPMNs

Postoperative recurrence was observed in 15 patients exclusively among those with I-IPMC (Table 5). Two patients with MI-IPMC suffered recurrence of MI-IPMC and invasive cancer in the remnant pancreas 36 and 48 months after surgery, respectively. At initial surgery, both patients had undergone PPPD for IPMNs in the pancreas head with negative surgical margins. The former underwent completion pancreatectomy in a second operation, and pathologic examination revealed another MI-IPMC in the remnant pancreas distant from the site of pancreato-jejunostomy. In the latter patient, recurrence of invasive ductal carcinoma was also found distant from the pancreato-jejunostomy, and additional partial resection of the remnant pancreas was performed. Both patients are currently doing well with no evidence of recurrence 8 and 20 months after the second operation, respectively. The remaining 13 recurrences were observed in patients with IC-IPMC. The site of recurrence was local (remnant pancreas) in 2 patients, LN in 2 patients, the lung in 1 patient, the liver in 4 patients, and peritoneal dissemination in 4 patients (Table 5). The time interval between surgery and recurrence was less than 20 months in all cases, with an especially short duration of 6.15 ± 0.82 months for patients with peritoneal dissemination.

## Analysis of the Pancreatic Surgical Margin

Intraoperative frozen section analysis of the pancreas margin was performed in 96 patients, and 17 patients needed additional pancreatic resection owing to the confirmed or suspected presence of cancer cells at the pancreatic surgical margin (Table 5). Additional resection was performed more frequently in patients with MI-IPMC and IC-IPMC than in those with noninvasive IPMN, regardless of IPMN size ($P = 0.007$). The final pancreatic margin status was negative in 75 patients, positive for IPMA in 25, borderline IPMN in 2, noninvasive IPMC in 1, and invasive carcinoma in 1.

## DISCUSSION

Many groups have investigated the malignant potential of IPMNs,[4,6,16,20,22–24] and the recent consensus is that its aggressiveness is dependent on the presence of invasive cancer, the extent of cancer invasion, and the biologic characteristics of the cancer cells.[2,3,8,10,14,15] However, no sufficient pathologic and presurgical staging system has yet been established for evaluating the malignant potential of I-IPMC. In this study, we examined 104 IPMNs surgically resected at the same hospital and proposed histopathologic criteria for classification of I-IPMC. I-IPMC shows heterogeneous features, which reflect the presence of heterogeneous cancer types with different biologic behaviors. Therefore, the criteria of MI-IPMC should differ in accordance with each histopathologic pattern of invasion. Our proposed

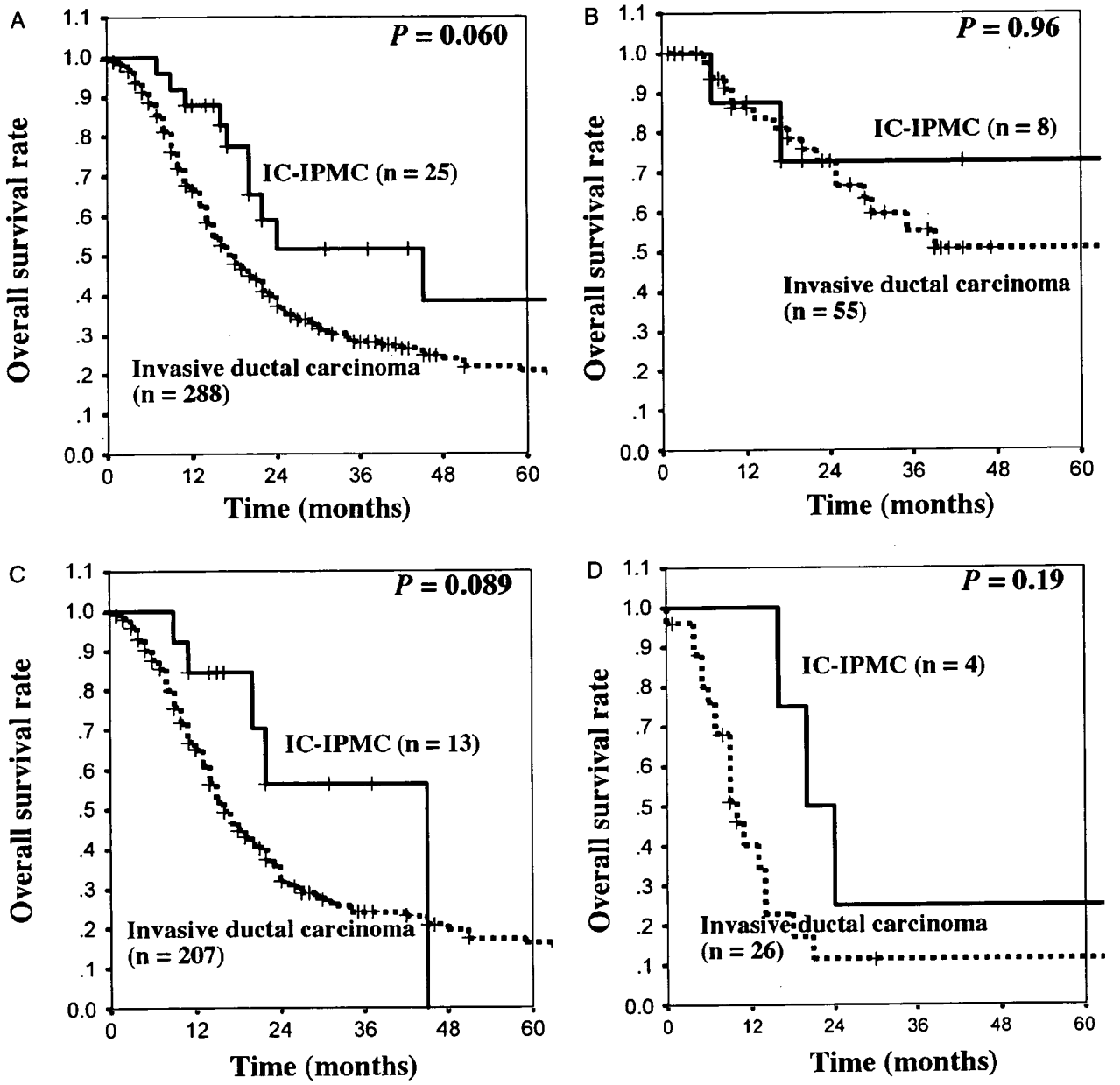



FIGURE 5. Kaplan-Meier survival curves of the 25 patients with IC-IPMC and the 288 patients with invasive ductal carcinoma of the pancreas. Comparison of overall survival of the patients with IC-IPMC and that of patients with conventional invasive ductal carcinoma at all stages (A), and in stage IA, IB, and IIA (B), stage IIB (C), and stage III and IV (D). Although the patients with IC-IPMC tended to have a better outcome than those with conventional invasive ductal carcinoma at each corresponding stage, the difference was not statistically significant.

criteria of invasiveness were successful in categorizing IPMCs in our series into noninvasive IPMC, MI-IPMC, and IC-IPMC. Patients with IC-IPMC had a significantly worse outcome than those with MI-IPMC. However, there was no difference in postoperative outcome between patients with MI-IPMC and those with noninvasive IPMC. This is the first report to propose practical criteria for MI-IPMC that can separate early-stage nonaggressive I-IPMC from total I-IPMC. Discrimination between MI-IPMC and IC-IPMC can provide important information for predicting the postoperative outcome of patients with IPMNs and also for deciding additional clinical management.

When IC-IPMCs were staged according to the size and spread of an invasive carcinoma component, the survival curve showed a similar decline to that of conventional invasive ductal carcinomas of the corresponding TNM stage, suggesting that it is the invasive

**TABLE 3.** Prognositic Factors of I-IPMCs in Univariate Analysis

| Variables | n | Survival Rate 1y | 3y | 5y | P (Log-rank Test) |
|---|---|---|---|---|---|
| Sex | | | | | 0.262 |
| M | 27 | 96.3 | 80.4 | 80.4 | |
| F | 24 | 91.7 | 70.4 | 41.5 | |
| Age (y) | | | | | 0.082 |
| ≤70 | 33 | 100.0 | 80.6 | 72.6 | |
| > 70 | 18 | 83.3 | 67.3 | 46.2 | |
| Tumor location | | | | | 0.937 |
| Ph included | 33 | 93.9 | 72.4 | 60.8 | |
| Ph excluded | 18 | 94.4 | 84.0 | 67.2 | |
| Tumor distribution | | | | | 0.821 |
| Confined in 1 segment | 35 | 91.4 | 75.7 | 63.2 | |
| Diffuse (≥ 2 segments) | 16 | 100.0 | 76.6 | 63.8 | |
| PV resection | | | | | 0.471 |
| + | 5 | 80.0 | 53.3 | 53.3 | |
| − | 46 | 95.7 | 78.0 | 63.0 | |
| Chief complaint* | | | | | 0.225 |
| + | 28 | 92.9 | 65.6 | 49.2 | |
| − | 23 | 95.6 | 90.0 | 81.0 | |
| Jaundice | | | | | **0.011** |
| + | 6 | 83.3 | 27.8 | 0.0 | |
| − | 45 | 95.6 | 80.7 | 66.2 | |
| IPMN type | | | | | 0.571 |
| MPD or mixed | 40 | 97.5 | 76.2 | 59.0 | |
| BD | 11 | 81.8 | 72.7 | 72.7 | |
| MPD diameter | | | | | 0.422 |
| ≤8 mm | 31 | 90.3 | 75.4 | 52.2 | |
| > 8 mm | 20 | 100.0 | 75.6 | 75.6 | |
| Additional resection of pancreas† | | | | | 0.864 |
| + | 14 | 92.9 | 63.7 | 63.7 | |
| − | 37 | 94.6 | 78.4 | 60.3 | |
| Surgical margin (except for pancreas margin)‡ | | | | | **< 0.001** |
| + or ± | 4 | 75.0 | 0.0 | 0.0 | |
| − | 47 | 95.7 | 84.4 | 69.1 | |
| Major vascular invasion (SMV, SPV, PV, or SPA) | | | | | **0.009** |
| + | 10 | 90.0 | 48.2 | 0.0 | |
| − | 41 | 95.1 | 82.0 | 71.2 | |
| Lymphatic invasion | | | | | **< 0.001** |
| + | 23 | 87.0 | 44.7 | 22.4 | |
| − | 28 | 100.0 | 95.5 | 81.7 | |
| Venous invasion | | | | | **0.006** |
| + | 26 | 88.5 | 53.5 | 42.8 | |
| − | 25 | 100.0 | 94.4 | 78.0 | |
| Intrapancreatic neural invasion | | | | | **< 0.001** |
| + | 24 | 87.5 | 52.7 | 39.5 | |
| − | 27 | 100.0 | 94.4 | 78.4 | |
| Local LN metastasis | | | | | **< 0.001** |
| + | 18 | 88.9 | 47.1 | 23.5 | |
| − | 33 | 97.0 | 88.9 | 76.4 | |
| Para-aortic LN metastasis | | | | | **< 0.001** |
| + | 3 | 100.0 | 0.0 | 0.0 | |
| − | 48 | 93.8 | 32.3 | 67.4 | |
| CEA (ng/mL) | | | | | 0.455 |
| ≤5 | 35 | 94.3 | 83.4 | 64.3 | |
| > 5 | 16 | 93.8 | 58.4 | 58.4 | |
| CA19-9 (U/mL) | | | | | **< 0.001** |
| ≤300 | 40 | 97.5 | 84.5 | 79.8 | |
| > 300 | 11 | 81.8 | 40.9 | 0.0 | |
| IPMN size (mm) | | | | | 0.552 |
| ≤40 | 15 | 93.3 | 70.2 | 43.9 | |
| > 40 | 36 | 94.4 | 78.2 | 72.2 | |
| IPMN size (mm) | | | | | 0.762 |
| ≤70 | 33 | 90.9 | 74.8 | 60.0 | |
| > 70 | 18 | 100.0 | 77.0 | 66.0 | |
| Size of invasive lesion (mm) | | | | | 0.001 |
| ≤20 | 32 | 96.9 | 88.7 | 75.1 | |
| > 20 | 19 | 89.5 | 48.7 | 32.4 | |
| Pathologic diagnosis | | | | | **< 0.001** |
| MI-IPMC | 26 | 100.0 | 94.7 | 78.6 | |
| IC-IPMC | 25 | 88.0 | 50.6 | 38.0 | |
| Histology of invasive cancer in I-IPMC | | | | | |
| Tubular adenocarcinoma§ | 29 | 89.7 | 61.8 | 54.1 | 0.065 |
| Pure mucinous carcinoma | 12 | 100.0 | 100.0 | 57.1 | |
| Tubular adenocarcinoma§ | 29 | 89.7 | 61.8 | 54.1 | **0.010** |
| Nontubular adenocarcinoma | 22 | 100.0 | 94.4 | 71.6 | |
| Pure mucinous carcinoma | 12 | 100.0 | 100.0 | 57.1 | 0.162 |
| Nonpure mucinous carcinoma | 39 | 92.3 | 68.6 | 62.9 | |
| Past history of another cancer in other organs | | | | | 0.316 |
| + | 10 | 90.0 | 72.0 | 54.0 | |
| − | 41 | 95.1 | 79.8 | 63.3 | |
| TNM stage | | | | | |
| MI-IPMC | 26 | 100.0 | 94.7 | 78.6 | |
| Stages IA, IB, and IIA | 8 | 87.5 | 70.0 | 70.0 | **0.040** |
| Stage IIB | 13 | 84.6 | 56.4 | 0.0 | 0.42 |
| Stages III and IV | 4 | 100.0 | 25.0 | 25.0 | 0.82 |

Statistically significant value is in bold characters.
*Diabetes mellitus exacerbation and jaundice included.
†Due to existence of neoplastic cells in pancreas margin in frozen section analysis.
‡Presence of invasive carcinoma cells in the stroma.
§Mixed tubular adenocarcinoma and mucinous carcinoma were included.
BD indicates branch duct; MPD, main pancreatic duct; Ph, pancreatic head; PV, portal vein.

carcinoma rather than IPMN itself that determines the prognosis.

In our series, none of the patients with MI-IPMCs showed LN metastasis, whereas the patients with IC-IPMCs had a high rate (68%) of LN metastasis. This finding implies that complete resection of a lesion without LN dissection may be sufficient for the treatment of MI-IPMC, whereas radical pancreatectomy with LN dissection is indicated for IC-IPMC. In this context, preoperative distinction between MI-IPMCs and IC-IPMCs is clinically very important.

**TABLE 4.** Multivariate Analysis of Effects of Clinicopathologic Factors on Postoperative Survival of I-IPMC

| | Hazard Ratio | 95% Confidence Interval | P* |
|---|---|---|---|
| IC-IPMC (vs. MI-IPMC) | 7.1 | 1.9-26.5 | < 0.001 |
| CA19-9 > 300 (U/mL) | 4.4 | 1.4-13.8 | 0.010 |

*P value was calculated by Cox hazards model (backward elimination method).

**TABLE 5.** Pancreatic Margin Status and the Recurrence of IPMNs After Surgery

| | IPMA or Borderline IPMN (n = 38) | Noninvasive IPMC (n = 15) | MI-IPMC (n = 26) | IC-IPMC (n = 25) | Total (n = 104) | P |
|---|---|---|---|---|---|---|
| Additional pancreas resection* | 3 | 0 | 5 | 9 | 17 | 0.007† |
| Final margin status | | | | | | 0.071 |
| Negative | 26 | 10 | 20 (2) | 19 (11) | 75 | |
| IPMA | 12 | 5 | 5 | 3 (1)‡ | 25 | |
| Borderline IPMN | 0 | 0 | 1 | 1 | 2 | |
| Noninvasive IPMC | 0 | 0 | 0 | 1 | 1 | |
| Invasive cancer | 0 | 0 | 0 | 1 (1)§ | 1 | |
| Recurrence | | | | | | |
| MI-IPMC (in the remnant pancreas) | 0 | 0 | 1 | 0 | 1 | |
| Invasive cancer (in the remnant pancreas) | 0 | 0 | 1 | 0 | 1 | |
| Local recurrence of invasive cancer | 0 | 0 | 0 | 2 | 2 | |
| Local LN | 0 | 0 | 0 | 2 | 2 | |
| Distant metastasis (lung or liver) | 0 | 0 | 0 | 5 | 5 | |
| Peritoneal dissemination | 0 | 0 | 0 | 4 | 4 | |
| Total | 0 | 0 | 2 | 13 | 15 | |

*Due to the presence of neoplastic cells in the pancreatic surgical margin in the frozen section analysis.
†Comparison between noninvasive IPMN and I-IPMC.
‡Liver metastasis.
§Local recurrence, numbers in the parentheses denotes the number of patients who developed recurrence after the operation.

Another significant finding was a predominantly high recurrence rate among patients with IC-IPMC (52%), compared with 2.5% for patients with noninvasive IPMN or MI-IPMC. In the latter group, recurrence was observed in the remnant pancreas distant from the cut end, suggesting that IPMC occurred multifocally. Although this recurrence rate is not as high as that reported previously,[4] careful follow-up seems to be necessary after surgery, especially in patients with IC-IPMCs.

Our criteria are not contradictory to the previous studies, in which the postoperative outcome of I-IPMC with pure mucinous carcinoma (colloid carcinoma) was better than that of patients with I-IPMC with tubular adenocarcinoma in the invasive lesion.[1,24] Tubular adenocarcinoma shows active infiltrative growth similar to conventional pancreatic ductal adenocarcinoma, suggesting that it rapidly grows and progresses into advanced cancer. In fact, tubular adenocarcinoma occurred at a higher rate in IC-IPMC than in MI-IPMC, and was an unfavorable prognostic factor ($P = 0.010$; Table 3). It has been reported that mucinous carcinoma associated with IPMN or mucinous cystic tumor has a better outcome than conventional ductal carcinoma. According to Adsay's criteria (a carcinoma with more than 80% of mucinous carcinoma is defined as pure mucinous carcinoma),[1] 12 I-IPMCs were diagnosed as pure mucinous carcinoma associated with IPMC in our series, which contained 11 MI-IPMC (5 with infiltrative growth of pure mucinous carcinoma, 2 with predominantly mucous rupture with cellular component, and 4 with expansive growth) and 1 IC-IPMC. Among these 12 patients with pure mucinous carcinoma associated with IPMC, 1 patient with MI-IPMC with infiltrative growth and 1 patient with IC-IPMC had recurrence of the carcinoma. Although 12 patients had the recurrent cancers and 10 of them died among 29 patients of I-IPMCs with tubular adenocarcinoma (8 in MI-IPMC and 21 in IC-IPMC). Patients with pure mucinous carcinoma as histologic type of invasive cancer tended to have better prognosis than patients with tubular adenocarcinoma as invasive cancer ($P = 0.065$; Table 3). Our study also suggested that some mucinous carcinoma has aggressive behavior. The prognosis of mucinous carcinoma in the other organs such as colon, has been reported to be worse than the ordinary adenocarcinoma, especially worse for mucinous carcinoma with rich cellular component.[17,21] In ductal carcinoma of the pancreas, mixed mucinous carcinoma with other histologic types of carcinoma (usually tubular adenocarcinoma) shows bad prognosis comparable with the other types of conventional ductal adenocarcinoma.[7,14] In this situation, it is desired that a diagnostic criterion is established to distinguish aggressive and nonaggressive mucinous carcinoma correctly. In this study, addition to the classification of tubular adenocarcinoma of the I-IPMC into aggressive and nonaggressive state, we also classified mucinous carcinoma relevant to clinical behavior based on the invasiveness and cellularity. Compared with mucous rupture, more aggressive mucinous carcinoma shows massive invasion with much more cancer cells floating and proliferating in mucus lakes, and is often accompanied by partial invasion of tubular adenocarcinoma.

Lymphatic, venous, and intrapancreatic neural invasion were frequently observed in IC-IPMC (Table 2) and were significant prognostic factors in I-IPMC (Table 3). In this study, we tried to select early-stage I-IPMC with nonaggressive characters from I-IPMCs with such worse prognostic factors. We successfully selected it by categorizing the infiltrating depth of cancer cells, which included lymphatic, venous, and/or neural invasion. Indeed, all the patients with MI-IPMC having vessel or neural invasion within 5-mm length from IPMC duct

showed good postoperative outcome. In addition, lymphatic, venous, and intrapancreatic neural invasion were not significant variables for the prognosis in multivariate analysis (Table 4).

The present results suggest that IC-IPMC (not MI-IPMC) should be currently paid attention as I-IPMC with aggressive characteristics. In this situation, preoperative detection of IC-IPMC can be beneficial for selecting the most ideal operative procedure, especially on considering additional LN dissection. We are now investigating possible criteria for classifying these cancers preoperatively, and our findings suggest that it may be feasible to use radiologic data for this purpose. Multidetector row computed tomography was found to be useful to distinguish IC-IPMC from MI-IPMC and noninvasive IPMNs with more than 80% sensitivity and 100% specificity in the study using 123 patients with IPMNs (manuscript in preparation).

In future, we would like to test our criteria using another large series of samples or in a prospective study, to obtain more watertight pathologic criteria for classification of I-IPMC.

## ACKNOWLEDGMENTS

*The authors thank Drs Tsuyoshi Sano, Yoshihiro Sakamoto, Hidenori Ojima, and Minoru Esaki for useful discussions.*

## REFERENCES

1. Adsay NV, Merati K, Nassar H, et al. Pathogenesis of colloid (pure mucinous) carcinoma of exocrine organs. *Am J Surg Pathol.* 2003; 27:571–578.
2. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms. Delineation of an 'intestinal' pathway of carcinogenesis in the pancreas. *Am J Surg Pathol.* 2004;28:839–848.
3. Biankin AV, Kench JG, Dijkman FP, et al. Molecular pathogenesis of precursor lesions of pancreatic ductal adenocarcinoma. *Pathology.* 2003;35:14–24.
4. Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology.* 2002;123:1500–1507.
5. Cho KR, Vogelstein B. Genetic alterations in the adenoma-carcinoma sequence. *Cancer.* 1992;70:1727–1731.
6. D'Angelica M, Brennan MF, Suriawinata AA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg.* 2004;239:400–408.
7. Fukushima N, Mukai K, Kanai Y, et al. Intraductal papillary tumors and mucinous cystic tumors of the pancreas. *Hum Pathol.* 1997;28:1010–1017.
8. Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch.* 2005;447:794–799.
9. Hiraoka N, Onozato K, Kosuge T, et al. Prevalence of FOXP3$^+$ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its precursor lesions. *Clin Cancer Res.* 2006;12:5423–5434.
10. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol.* 2004;28:977–987.
11. International Union Against Cancer (UICC). *TNM Classification of Malignant Tumors.* 6th ed. New York, NY: Wiley-Liss; 2002.
12. Japan Pancreas Society. *Classification of Pancreatic Cancer.* 2nd ed. Tokyo, Japan: Kanehara; 2003.
13. Klöppel G, Solcia E, Longnecker DS, et al. *Histological Typing of Tumors of the Exocrine Pancreas, World Health Organization International Histological Classification of Tumors.* 2nd ed. Berlin, Germany: Springer; 1996.
14. Klöppel G, Hruban RH, Longnecker DS, et al. Ductal adenocarcinoma of the pancreas. In: Hamilton SR, Aaltonen LA, eds. *Pathology and Genetics. Tumours of the Digestive System. World Health Organization Classification of Tumours.* Lyon, France: IARC Press; 2000:221–230.
15. Longnecker DS, Adler G, Hruban RH, et al. Intraductal papillary-mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, eds. *Pathology and Genetics. Tumours of the Digestive System. World Health Organization Classification of Tumours.* Lyon, France: IARC Press; 2000:237–240.
16. Maire F, Hammel P, Terris B, et al. Prognosis of malignant intraductal papillary mucinous tumours of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. *Gut.* 2002;51:717–722.
17. Minsky BD, Mies C, Rich TA, et al. Colloid carcinoma of the colon and rectum. *Cancer.* 1987;60:3103–3112.
18. Mizuta Y, Akazawa Y, Shiozawa K, et al. Pseudomyxoma peritonei accompanied by intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology.* 2005;5:470–474.
19. Nakagohri T, Asano T, Kenmochi T, et al. Long-term surgical outcome of noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma of the pancreas. *World J Surg.* 2002;26:1166–1169.
20. Raimondo M, Tachibana I, Urrutia R, et al. Invasive cancer and survival of intraductal papillary mucinous tumors of the pancreas. *Am J Gastroenterol.* 2002;97:2553–2558.
21. Ronnett BM, Zahn CM, Kurman RJ, et al. A Clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". *Am J Surg Pathol.* 1995;19:1390–1408.
22. Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg.* 2004;239:677–678.
23. Shimada K, Sakamoto Y, Sano T, et al. Invasive carcinoma originating in an intraductal papillary mucinous neoplasm of the pancreas: a clinicopathologic comparison with a common type of invasive ductal carcinoma. *Pancreas.* 2006;32:281–287.
24. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg.* 2004;239:788–789.
25. Suzuki Y, Atomi Y, Sugiyama M. Cystic neoplasm of the pancreas: a Japanese multi-institutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. *Pancreas.* 2004;28:241–246.
26. Wells M, Östör AG, Crum CP, et al. Epithelial tumours. In: Tavassoli FA, Devilee P, eds. *Pathology and Genetics of Tumours of the Breast and Female Genital Organs. World Health Organization Classification of Tumours.* Lyon, France: IARC Press; 2003: 262–269.
27. Yamao K, Ohashi K, Nakamura T, et al. The prognosis of intraductal papillary mucinous tumors of the pancreas. *Hepato-gastroenterology.* 2000;47:1129–1134.