Intraductal Papillary Mucinous Tumors of the Pancreas Comprise 2 Clinical Subtypes

Differences in Clinical Characteristics and Surgical Management

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Hypothesis: Intraductal papillary mucinous tumors (IPMTs) of the pancreas may be meaningfully construed as representing 2 clinically distinct subtypes: main duct tumors (MDT) and branch duct tumors (BDT).

Design: Retrospective study.


Patients and Intervention: We reviewed diagnostic findings and late results of surgical treatment in 30 patients with IPMT.

Results: The tumor was located in the head of the pancreas more often in BDT than in MDT (65% [11/17] and 23% [3/13], respectively). Of the 13 patients with MDTs, 12 (92%) had intraductal papillary adenocarcinoma (non-invasive and minimally invasive types) and/or carcinoma in situ (carcinoma in situ: low papillary and/or flat tumor cells), and 3 (23%) had stromal invasion. Of the 17 patients with BDTs, 5 (29%) had intraductal papillary adenocarcinoma and/or carcinoma in situ. Two pancreatoduodenectomies and 8 pylorus-preserving pancreatoduodenectomies were performed in 10 of the 17 patients with BDTs, distal pancreatectomy in 7 patients with MDTs, and total pancreatectomy in 4 patients with MDTs. The 5-year survival rates were 47% for MDT and 90% for BDT. Four of 6 patients with MDTs who died had local recurrence. One patient died of liver metastasis and 1 of esophageal cancer. Only 1 patient with BDT of the 2 who died had recurrent disease.

Conclusions: Intraductal papillary mucinous tumors may be composed of 2 clinically distinct subtypes: MDTs and BDTs. Initially, although distal pancreatectomy can be recommended for most MDTs, the need for cancer-free margins in this more aggressive type may necessitate total pancreatectomy. Pylorus-preserving pancreatoduodenectomies is recommended for most BDTs, but, because these tumors are more often adenomas, a good prognosis can be expected.

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Improved tumor imaging has greatly facilitated the discovery of cystic lesions in the abdomen. Among the neoplastic cysts of the pancreas, intraductal papillary mucinous tumors (IPMTs), often described as intraductal papillary neoplasms (IPNs) or mucinous ductal ectasia (MDE), have attracted much attention since the report in 1982 of Ohhashi et al, who proposed that they constituted a clinical entity distinct from mucinous cystic neoplasms. Intraductal papillary mucinous tumors are distinguished from the more common cystic neoplasms because they can communicate with the main and/or branch ducts and have a far more favorable prognosis. Although many reports about this tumor have appeared, various issues, such as symptoms, diagnosis, prognosis, and selection of the most appropriate mode of surgical management, remain to be clarified. In terms of classification, there has been controversy about whether IPN and MDE represent 2 distinct tumors or the same clinicopathologic entity. Although Rivera et al concluded that they were almost identical and should therefore be subsumed by the more encompassing term intraductal papillary mucinous tumors, they reported that MDE tumors involved the head of the pancreas more often than IPN tumors.

To determine whether practical distinctions remain to be made among these tumors, 30 patients diagnosed with IPMT were divided into 2 groups according to whether the predominant area of involvement was the main duct or branch ducts, based on endoscopic retrograde cholangiography (ERCP) findings, tumor imaging diagnosis, and surgical specimens. We compared the clinical features, histopathological characteris-
PATIENTS AND METHODS

The clinical characteristics of IPMT of the pancreas were investigated in 30 patients treated in our department between January 1988 and December 1996. The diagnosis of IPMT was confirmed histologically according to the guidelines of the Japan Pancreas Society. In the Japanese classification, IPMTs are sub-classified into intraductal papillary adenoma, intraductal papillary adenocarcinoma, and carcinoma in situ. These tumors arise from the epithelial lining of the pancreatic main and branch ducts. Intraductal papillary adenocarcinoma is characterized as prominent papillary structures lined by tall neoplastic cells, and can be further classified into a noninvasive type and a minimally invasive type. On the other hand, carcinoma in situ is limited to within the pancreatic duct, and the epithelium is low papillary and/or flat. The presence of enlarged nuclei of variable size, prominent nucleoli, and nuclear pseudostratification indicates a malignant neoplasm. Patients with cystic tumors that did not communicate with the main or branch ducts were excluded from this study.

These patients were divided into 2 groups, main duct tumors (MDTs) and branch duct tumors (BDTs), according to the predominant area of involvement as determined by our previously reported system. Main duct tumors exhibited features on gross examination such as a uniformly dilated or focally dilated main duct. Branch duct tumors were characterized on gross examination by cystic subbranches or dilated sub-branches, most frequently in the uncinate process. There were 13 patients in the MDT group and 17 patients in the BDT group. We compared the 2 groups on clinical presentation, findings on tumor imaging, histopathological characteristics, and cumulative survival rates.

Survival was calculated by the Kaplan-Meier method and compared by log-rank test. Other comparisons were performed using the t test or \( \chi^2 \) test. Statistical significance was defined as \( P < .05 \).

RESULTS

CLINICAL PRESENTATIONS

The clinical presentations are shown in Table 1. In both groups, the number of male patients was 4 times greater than the number of female patients. The mean age of the patients was 64 years in both groups. More than 60% of the patients had complained of epigastric pain and about 30% of the patients had back pain. A history of acute pancreatitis and diabetes mellitus was significantly more common in the MDT group. The duration of symptoms was longer (3.6 years on average) for patients in the MDT group. Patients in the MDT group had suffered from epigastric pain that mimicked acute pancreatitis for more than 3 years.

### Table 1. Clinical Presentation of Intraductal Papillary Mucinous Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Main Duct Type (n = 10)</th>
<th>Branch Duct Type (n = 14)</th>
<th>Total (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>9/12 (75)</td>
<td>8/12 (67)‡</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4/12 (33)</td>
<td>3/14 (21)</td>
<td>7/26 (28)</td>
</tr>
<tr>
<td>History of acute pancreatitis†</td>
<td>5/10 (50)</td>
<td>3/14 (21)</td>
<td>8/24 (33)</td>
</tr>
<tr>
<td>Diabetes mellitus§</td>
<td>6/12 (50)</td>
<td>9/14 (64)</td>
<td>15/26 (58)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>3.6 ± 3.6</td>
<td>1.9 ± 2.6</td>
<td>2.7 ± 3.1</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
†History of acute pancreatitis was defined as upper abdominal pain with an elevated serum amylase level. The patient was diagnosed as having diabetes mellitus when a typical diabetes mellitus pattern was detected by oral glucose tolerance test.
§Differs from branch duct type (\( P = .02 \)).
‡Differs from branch duct type (\( P = .03 \)).

### Table 2. Endoscopic Retrograde Cholangiopancreatography Findings for Intraductal Papillary Mucinous Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Finding</th>
<th>Main Duct Type (n = 10)</th>
<th>Branch Duct Type (n = 14)</th>
<th>Total (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling defects, No. (%)</td>
<td>6/10 (60)</td>
<td>11/14 (78)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>6/10 (60)</td>
<td>5/14 (36)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Branch pancreatic duct</td>
<td>0 (0)</td>
<td>6/14 (43)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Papillary growth, No. (%)</td>
<td>3/10 (30)</td>
<td>0/14 (0)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>3/10 (30)</td>
<td>0/14 (0)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Branch pancreatic duct</td>
<td>0 (0)</td>
<td>0/14 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Differs from branch duct type (\( P = .02 \)).
†Differs from main duct type (\( P = .04 \)).

ERCP FINDINGS

Endoscopic retrograde cholangiopancreatography findings in the 24 patients for whom ERCP could be performed successfully were compared between the 2 groups (Table 2). Diffuse dilation was significantly more common in the MDT group. The size of the dilated main pancreatic duct was 7 mm in 1 patient and more than 10 mm in 7 patients in the MDT group. For patients in the BDT group, however, the main duct was never dilated more than 5 mm. Cystic dilations or clusters of small cysts in the branch pancreatic ducts were found more often in the patients in the BDT group. Swelling of the papilla of Vater, dilation of the orifice of the papilla, or mucin secretion from the orifice was detected in 5 patients (50%) in the MDT group. Filling defects of the pancreatic ducts...
Table 3. Computed Tomography, Magnetic Resonance Imaging, or Ultrasonography, and/or Findings for Intraductal Papillary Mucinous Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Duct Type</th>
<th>Main Pancreatic Duct (n = 26)</th>
<th>Branch Pancreatic Duct (n = 26)</th>
<th>Total (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic dilation</td>
<td>10 (38)†</td>
<td>4 (29)</td>
<td>14 (54)</td>
</tr>
<tr>
<td>Clusters of small cysts</td>
<td>6 (50)</td>
<td>9 (64)</td>
<td>15 (58)</td>
</tr>
<tr>
<td>Filling defects, No. (%)</td>
<td>6 (50)</td>
<td>6 (43)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>5 (42)</td>
<td>0 (0)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Branch pancreatic duct</td>
<td>1 (10)</td>
<td>6 (43)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Papillary growth, No. (%)</td>
<td>4 (33)</td>
<td>5 (36)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>3 (25)</td>
<td>0 (0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Branch pancreatic duct</td>
<td>1 (10)</td>
<td>5 (36)</td>
<td>6 (23)</td>
</tr>
</tbody>
</table>

* When the size of main pancreatic duct was measured to be more than 5 mm on computed tomographic scan and more than 4 mm on ultrasonography, the main pancreatic duct was judged as dilated.
† Differs from branch duct type (P = .005).
‡ Differs from main duct type (P = .02).

were found in more than 60% of patients in both groups. Filling defects were found in the main pancreatic duct for patients in the MDT group and in both ducts for patients in the BDT group. The filling defect was papillary growth of the main pancreatic duct in 3 patients (30%) in the MDT group.

IMAGING DIAGNOSIS FINDINGS

When the size of the main pancreatic duct was found to be more than 5 mm on computed tomographic (CT) scan and more than 4 mm on ultrasonography, it was judged as dilated. Dilatation of the main pancreatic duct was detected in 83% of the patients (10/12) in the MDT group. Using these imaging techniques for the BDT group, we found that the main pancreatic duct was dilated in 29% of patients (4/14), but never more than 5 mm. Cystic dilation of the branch ducts was observed in 11 patients (7%) and clusters of small cysts in 9 patients (64%) in the BDT group, and these features were observed without dilation of the main pancreatic duct in 10 (71%) of the same patients. Filling defects of the pancreatic ducts were found in about half of the patients in both groups, and these were diagnosed as papillary tumor growth in more than two thirds of the patients who had filling defects (4/6 for MDT group and 5/6 for BDT group). Filling defects in the MDT group occurred mostly in the main pancreatic duct, and those in the BDT group were detected only in the branch pancreatic duct (Table 3). The diagnostic accuracy rate of the preoperative tumor imaging for the histologically determined principal location of the tumors (main pancreatic duct vs branch pancreatic duct) was 77% (10/13) in the MDT group and 94% (15/16) in the BDT group.

TUMOR MARKER LEVEL

Serum carcinoembryonic antigen levels were elevated in 3 patients: 2 (15%) in the MDT group and 1 (6%) in the BDT group. The CA-19-9 level was elevated in 7 patients, 4 (31%) in the MDT group and 3 (18%) in the BDT group. These elevations were mild in most patients.

SURGICAL TREATMENT AND CLINICOPATHOLOGICAL FEATURES

Distal pancreatectomy or total pancreatectomy was performed far more often for patients in the MDT group than for those in the BDT group (Table 4). In contrast, pancreateoduodenectomy was performed in 10 of the 16 patients who underwent operations in the BDT group. Tumors in the MDT group were found more frequently in the body or tail of the pancreas, and 23% (n = 3) of these were diffuse. In contrast, tumors in the BDT group were most often found in the head of the pancreas, usually in the uncinate process. The mean size of the tumors did not differ between the 2 groups. The mean size of intraductal papillary adenocarcinoma or carcinoma in situ was significantly larger than that of the 12 intraductal papillary adenomas (28.9 ± 15.4 mm and 14 ± 8.5 mm, respectively). The incidence of adenocarcinoma and/or carcinoma in situ was significantly higher in the patients in the MDT group. Stromal invasion was detected in 3 patients (23%) in the MDT group but in only
1 patient (6%) in the BDT group. In the histopathological analyses of fixed specimens from the pancreatic cut end, carcinoma cells were found in 6 (46%) of the 13 patients with MDT, in spite of the fact that the corresponding intraoperative frozen sections were negative. Intraductal papillary adenoma was found in the fixed specimens from the pancreatic cut end in 4 (25%) of the patients with BDTs but in none of the patients with MDTs.

SURVIVAL RATES

In the MDT group, the follow-up period ranged from 8 to 68 months (median, 37 months; mean ± SD, 35 ± 22 months). In the BDT group, the follow-up period ranged from 6 to 82 months (median, 52 months; mean ± SD, 48 ± 24 months). The 5-year survival rate of patients in the BDT group was 90%, but it was only 47% for the patients in the MDT group (Figure).

There were 6 deaths in the MDT group: 3 patients died of local recurrence (pancreatic remnant and pancreatic retroperitoneal tissue), 1 of local recurrence with liver metastasis, 1 of bone metastasis, and 1 of esophageal cancer. Of the 4 patients who died of local recurrence, 2 underwent total pancreatectomy, 1 pancreatoduodenectomy, and 1 distal pancreatectomy. Stomal invasion was found in 3 of the 4 patients in the MDT group who died of local recurrence. Of the 2 patients who died in the BDT group, 1 died of liver cirrhosis and 1, in whom the original tumor was papillary adenocarcinoma with stromal invasion, died of liver metastasis. Of the 8 patients who died, only 1 had a pancreatic cut end positive for adenocarcinoma cells; this patient was from the MDT group (Table 5).

**COMMENT**

Although IPMTs have some characteristics that are similar to those of mucinous cystic neoplasms, the histopathological features are very different.1,4,7-12,19 Mucinous cystic tumors are intrinsically malignant or have malignant potential even though they grow slowly.20 They often occur in middle-aged women, with the chief complaints being pain and tumor mass in the epigastrium. These tumors are usually located in the tail of the pancreas and are composed of well-circumscribed, mucinous multilocular or unilocular cysts with a mean size of 7 to 10 cm.21,22 In contrast, IPMTs develop more frequently in older men and are often located in the head of the pancreas. The average size (3-4 cm) is much smaller than that of mucinous cystic tumors. Most patients present with acute or chronic pancreatitis-like pain and diabetes with a long duration of symptoms.1,3,6,7,23

Although IPMTs have been subclassified into MDTs and BDTs by the Japan Pancreas Society, this distinction has not been generally recognized outside of Japan.1,3,15,18,19,24-26 Using ERCP or magnetic resonance cholangiopancreatography, it is not difficult to distinguish these 2 subtypes.13,19 Rivera et al,1 reviewing a single institutional experience with MDE and IPN, compared the clinicopathologic features of the 2 groups of tumors and found that MDE and IPN were almost identical, possibly representing 2 points on a spectrum of pancreatic intraductal neoplasms. However, as noted by the authors, the MDE tumors more frequently involved the head of the pancreas and seemed to be identical to what is referred to as BDT in Japan, with IPN corresponding to MDT. In the present study, the clinicopathologic features of IPMTs were investigated to determine whether they actually comprise 2 clinically distinct subtypes.

The locations of the tumors tended to differ; MDTs were more frequently found in the body or tail of the pancreas (77% [10/13]) and BDTs in the head of the pancreas (65% [11/17]), especially in the uncinate process. A long history of diabetes or upper abdominal pain mim-
icking acute pancreatitis may therefore suggest that the tumor is located in the main pancreatic duct.

In the ERCP findings, diffuse dilation of the main pancreatic duct was most often found in the MDT group, whereas the BDT group was characterized by cystic dilation or clusters of small cysts in the branch ducts. These findings are compatible with the CT findings of Itoh et al,24 summarized as follows: the MDTs consist of a cystic mass that contains excrecent nodules and/or septa and is in or communicates with the dilated main pancreatic duct, which is markedly dilated over its entire length; BDTs were composed of clustered small cysts of approximately the same diameter (1-2 cm). Excrecent nodules were not always seen, and the part of the main duct near the lesion was often slightly diluted. The macroscopic findings corresponded to these CT findings.24 In our CT findings, dilation of the main duct was also found in most patients in the MDT group, and cystic dilation of the branch ducts characteristically occurred in the BDT group. We believe that clinical differentiation between the 2 subtypes can be done preoperatively in most patients. Actually, in this study, the diagnostic accuracy rate of the preoperative imaging was 77% (10/13) in the MDT group and 94% (16/17) in the BDT group.

Clinical differentiation between MDTs and BDTs is important because of the very different prognoses of these 2 subtypes. In the present study, malignant tumors with carcinoma cells were more frequently found in the MDT group than in the BDT group, in which adenomas were predominant. This difference was well reflected in the corresponding survival rates. In addition, several other reports have shown that the rates of malignancy were higher for MDTs (67%-100%) than for BDTs (0%-47%).13,24-26 In a study of 35 patients with IPMT in which the clinicopathologic characteristics were compared between MDTs and BDTs, malignant lesions were found in 83% of patients (5/6) with MDTs. In contrast, malignant tumors were found in 43% of the patients (12/28) with BDTs. Additionally, it was noted that all BDTs larger than 4 cm were malignant; stromal invasion was found in 33% of patients (5/15) with adenocarcinoma.27

Our results might also suggest an association between diffuse dilation of the main duct and malignancy since, in the MDT group, the rate of malignancy was 92% (12/13) and the rate of diffuse dilation was 83% (10/12); 60% (3/5) of patients in the BDT group who had malignant lesions also had diffuse dilation or papillary growth of the cyst wall (data not shown). These findings support the recommendation of Kobayashi et al28: surgical resection should be performed as soon as possible when dilation of the main duct, papillary growth, irregularity, or thickening of the cyst wall is detected by endoscopic ultrasonography.

Since it is possible that the malignant potential of IPMT can be explained by a sequential change from hyperplasia to cancer, it is important to emphasize the possibility of multicentric carcinoma in this type of tumor.13,20,26 In our previous 3-dimensional, computerized reconstruction study, it was revealed that, in MDTs with diffuse dilation of the main duct, an extremely wide ductal area is likely to be involved; carcinoma cells could be found extending as much as 2 cm into undilated areas, and neoplastic cells were also found in segments without remarkable dilation.13 The results of our present study also suggest that, with MDTs, there may often be carcinoma cells remaining in the cut end of the pancreatic remnant. Therefore, for MDTs, excision should include not only the diluted area but also the parenchymal zone corresponding to the dilated duct. Since intraoperative section studies cannot always guarantee a cancer-free surgical margin, the more aggressive nature of MDTs compared with BDTs may sometimes justify total pancreatectomy. In such cases, quality of life must certainly be taken into account, especially with very old patients or those with other impairments, because the operation entails so much morbidity. Quality of life may also sometimes be a factor in the election of surgery for BDTs; for example, in elderly patients with minimal symptoms, it might be better to wait and observe carefully, always mindful of the premalignant state may suddenly change to malignant, necessitating resection.

Intraductal papillary mucinous tumors, particularly those that can be subclassified as MDTs, can involve stromal invasion and distant metastasis.3,7,13,22 Milchgrub et al22 reported stromal invasion and lymph node metastasis in 3 of 4 patients presenting with multicentric intraductal papillary carcinomas in the main pancreatic duct. In the present study, stromal invasion was found in 3 of the patients with MDTs and in 1 patient with a BDT. Such invasion was well reflected by the type of recurrence because, of the 4 patients with MDTs who died of local recurrence, 3 had stromal invasion. In addition, the patient with an MDT who died of bone metastasis and the patient with a BDT who died of liver metastasis also had stromal invasion. Accordingly, both types of tumors can be malignant, but MDTs are much closer to the common invasive ductal carcinoma of the pancreas in terms of aggressiveness, metastatic potential, and survival rates. More effective therapeutic modalities, including extended resection or chemoradiation therapy, may have to be considered for this type of tumor.

Intraductal papillary mucinous tumors may comprise 2 clinically distinct subtypes: MDTs and BDTs. Distal pancreatectomy can be recommended for most MDTs, for which total pancreatectomy may sometimes be required, depending on the degree of diffuse dilation or when no cancer-free margin can be found. For BDTs, which occur most frequently in the head, pancreaticoduodenectomy is usually recommended. These 2 subtypes can be distinguished preoperatively in most cases.

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References


