Intraductal Papillary-Mucinous Tumors of the Pancreas

Predictive Criteria of Malignancy According to Pathological Examination of 53 Cases

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Background: One of the main problems in the management and treatment of intraductal papillary-mucinous tumors is the lack of a reliable predictive factor for malignancy.

Hypothesis: Surgical treatment could be adapted to macroscopic criteria (presence of mural nodules and diameter of the pancreatic duct and of the lesion) or to tumor location (main duct, branch duct, or combined lesions) associated with benign or malignant forms.

Design: Retrospective study.

Setting: Two university and tertiary referral centers.


Results: Macroscopic analyses of tumors showed 6 main duct lesions, 12 branch duct lesions, and 35 combined lesions. A carcinoma was present in 33 cases (62%): 22 (41%) were invasive and 11 (21%) were noninvasive; 9 (17%) were borderline tumors and 11 (21%) were benign. Carcinoma and invasive carcinoma forms were less frequent in branch duct lesions ($P<.001$ and $P=.009$, respectively). Mural nodules were more frequent in carcinomas ($P=.006$) and invasive carcinomas ($P<.001$), with a positive predictive value of malignancy of 81%. The diameter of lesions (branch duct lesion $\geq 30$ mm) or main duct (main pancreatic duct $\geq 15$ mm in combined or main pancreatic duct lesions) did not correlate with malignancy.

Conclusions: No carcinoma occurred in branch duct types smaller than 30 mm without mural nodules. Limited resection may be appropriate only in this type of tumor.

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Methods

Fifty-three consecutive patients, including 31 men and 22 women with a median age of 61.2 years (range, 38-78 years), who underwent a pancreatic resection for IPMT in 2 institutions between January 1, 1985, and December 31, 2000, were included in this study. Operative procedures were the following: total pancreatectomy $n=4$, pylorus-preserving pancreaticoduodenectomy $n=30$, pancreatoduodenectomy with antrectomy $n=6$, spleen-preserving distal pancreatectomy $n=7$, distal pancreatectomy $n=4$, and middle resection of the pancreas $n=2$.

Pathological examination after section of the pancreatic specimen along the main pancreatic duct and dilated branch ducts enabled 4 criteria to be defined: (1) IPMT subtype according to the classification used by...
The correlations between these criteria and the epithelial intraductal lesions were studied. Intraductal lesions were classified into 4 grades, according to the WHO classification, and the most severe grade of epithelial dysplasia was taken into account. According to previous assessment of imaging findings indicative of carcinoma, we retained as threshold values a main pancreatic duct diameter of 15 mm or more for the main and combined pancreatic duct types, a cystic lesion diameter of 30 mm or more for branch duct types, and obvious mural nodules equal to or greater than 3 mm for all of the types. A second pathological examination took into account all of the resected specimen.

Differences between categorical variables were evaluated by \( \chi^2 \) test or Fisher exact test. Differences were considered significant at \( P < .05 \).

### RESULTS

The IPMTs were classified as invasive carcinoma in 22 cases (41%), noninvasive carcinoma (carcinoma in situ or severe dysplasia) in 11 cases (21%), borderline (moderate dysplasia) in 9 cases (17%), and adenoma (mild dysplasia) in 11 cases (21%). A malignant form was found in 73% of cases (24/33) in patients aged 60 years or older and in 45% (9/20) of the remaining patients \( (P = .04) \).

There were 6 cases of main duct type (11%), 12 cases of branch duct type (23%), and 35 cases of combined duct type (66%). The numbers of malignant or invasive forms were similar according to right or left location of the tumor. In fact, a malignant form was noted in 61% (22/36) of cases with a right location and in 53% (6/11) in cases with a left location. Furthermore, an invasive form was found in 44% (16/36) with right location and in 27% (3/11) with left location (middle and total pancreatectomies were excluded).

The correlations between the histologic grade and the classification used by Sugiyama and Atomi\(^2\) are shown in Table 1. The rate of malignant tumors was significantly higher in the main duct type (83%; \( P = .02 \)) and in the combined type (74%; \( P = .002 \)) compared with the branch duct type (17%). Among the malignant forms, the rate of invasive carcinomas was significantly higher in the main duct type (83%; \( P = .004 \)) and in the combined duct type (46%; \( P = .04 \)) compared with the branch duct type (8%). The rate of carcinoma ranged from 17% to 76% according to the absence or presence of main pancreatic duct lesions \( (P < .001) \), and the rate of invasive carcinoma ranged from 8% to 51% according to the absence or presence of main pancreatic duct lesions \( (P = .009) \). A benign form (adenoma and borderline) was more frequent in the branch duct type (83%) than in the main duct type (17%; \( P = .02 \)) or the combined type (26%; \( P = .002 \)).

A diameter of the main pancreatic duct equal to or greater than 15 mm was observed in 16 cases of main duct and combined types \( (n = 41) \) and was not significantly associated with a carcinoma (Table 2). When the diameter was equal to or greater than 15 mm, the tumors were malignant in 88% (14/16) and invasive in 50% (8/16) of cases, but when the diameter was less than 15 mm, the tumors were malignant in 68% (17/25) and invasive in 52% (13/25). We noted 3 noninvasive carcinomas and 2 invasive carcinomas with a diameter of the main pancreatic duct less than 15 mm without any mural nodules (Table 3).

Comparison between the histologic grade and the size of the cystic dilation in the branch duct type did not disclose any correlation. Nevertheless, a carcinoma was discovered in only 2 cases with a cystic dilation less than 30 mm and was associated with mural nodules (Table 3). All 7 patients with a dilation less than 30 mm and without mural nodules were still alive with no evidence of disease after a mean \( \pm \) SD of 3.4 \( \pm \) 1.4 years of follow-up.

Mural nodules were found in 26 cases (49%; Table 3) and were more frequent \( (P = .006) \) in malignant forms (64% [21/33]) than benign forms (25% [5/20]). An in-

### Table 1. Histologic Stage Compared With Morphologic Classification

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Malignant Forms, No.</th>
<th>Adenoma (Mild Dysplasia)</th>
<th>Borderline (Moderate Dysplasia)</th>
<th>Noninvasive Carcinoma (Severe Dysplasia or In Situ Carcinoma)</th>
<th>Invasive Carcinoma (Microinvasive Carcinoma or Invasive Carcinoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main duct type</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Branch duct type</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combined type</td>
<td>35</td>
<td>5</td>
<td>4</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 2. Histologic Stage Compared With Size and Type of Lesion

<table>
<thead>
<tr>
<th>Size, mm</th>
<th>Benign Forms, No.</th>
<th>Malignant Forms, No.</th>
<th>Adenoma (Mild Dysplasia)</th>
<th>Borderline (Moderate Dysplasia)</th>
<th>Noninvasive Carcinoma (Severe Dysplasia or In Situ Carcinoma)</th>
<th>Invasive Carcinoma (Microinvasive Carcinoma or Invasive Carcinoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main duct type or combined type</td>
<td>15 or more</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Branch duct type</td>
<td>30 or more</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
vative carcinoma was more often associated (P<.001) with mural nodules (77% [17/22]) than the benign forms (25% [5/20]) or all the other cases (29% [9/31]).

The discovery of mural nodules was a predictive factor for malignancy, with a sensitivity of 64%, a specificity of 75%, a positive predictive value of 81%, and a negative predictive value of 56% (Table 4).

Correct prediction of malignancy, especially for invasive adenocarcinomas, remains one of the major problems in the management and optimal treatment of IPMTs. Since survival after surgery is closely related to the presence of invasive carcinoma, it is of major importance to point out the predictive criteria of malignancy, particularly of invasive carcinoma. This study confirms the high rate of malignant tumors (62%), including noninvasive (21%) and invasive (41%) carcinomas, according to recent reports. In a literature review, the prevalence of malignant tumors reached 72%, but in other reports, the rate of malignancy was less than 50%. It is essential to focus on the incidence of invasive adenocarcinomas (from 42% to 43%) and to classify the remaining patients as having dysplasia. According to the WHO classification, patients with severe dysplasia or in situ carcinoma are assigned to the noninvasive carcinoma group. In our study, patient characteristics were similar to those in previous reports concerning mean age and male predominance (sex ratio, 1.4). Like Paye et al and Yamao et al, we noted a correlation between age and malignancy.

The IPMTs are classified into 3 subtypes, based on the site of duct involvement by tumor (main duct type, branch duct type, and combined duct type with both main and branch duct involvement). According to this classification, the frequency of different subtypes is variable: 29% to 47% for main duct type, 14% to 29% for combined duct type, and 30% to 57% for branch duct type. In our study, the histologic findings differed, with a higher rate of combined duct type (66%) and a lower rate of main duct type (11%) and branch duct type (23%). The differences in frequency of different subtypes could be explained by a second and careful pathological examination, which showed the frequent association of lesions within both the main and branch ducts and an increase in the number of combined duct types at the expense of the rate of main and branch duct types. These features are in agreement with the recent classification into 2 types according to the presence or absence of lesions of the main pancreatic duct. According to histologic findings, lesions of the main duct type are predominant (60%-78%), whereas lesions of the main pancreatic duct (isolated or associated) were discovered in 77% of cases. It is debatable whether a main duct type can exist without branch duct lesions.

The rate of carcinomas is significantly higher in IPMTs with a tumor in the main pancreatic duct, including main and combined duct types (76% in our series), and attains 92% in some reports. The rate of invasive carcinoma ranges from 13% to 56% according to the absence or presence of main pancreatic duct lesions. In our series, the same rate ranges from 8% to 51% (P=.009). Other groups have shown a better histologic form in the case of branch duct lesions as well as a better prognosis.

In Sugiyama and Atomi’s study, the main pancreatic duct diameter equal to or greater than 15 mm (for main and combined duct types) and size of the cystic tumor equal to or greater than 30 mm (for branch duct type) showed a high prevalence of adenocarcinoma. They chose the threshold value of 15 mm for the main pancreatic duct, because 70% of tumors with a main pancreatic duct diameter of less than 15 mm were benign, whereas 87% of those with a diameter of 15 mm or more were malignant. In the case of branch duct–type tumors, 89% of tumors larger than 30 mm were malignant, in contrast to a rate of 29% for tumors smaller than 30 mm, with no case of invasive carcinoma. The findings were different in our series. The risk of malignancy was not significantly different when the main pancreatic duct diameter was equal to or greater than 15 mm (88%) or less than 15 mm (68%). A diameter equal to or greater than 10 mm is probably more reliable in defining the risk of malignancy.

Table 3. Presence and Proportion of Mural Nodules According to Histologic Stage, Size, and Type of Lesion

<table>
<thead>
<tr>
<th>Size, mm</th>
<th>Adenoma (Mild Dysplasia)</th>
<th>Borderline (Moderate Dysplasia)</th>
<th>Noninvasive Carcinoma (Severe Dysplasia or In Situ Carcinoma)</th>
<th>Invasive Carcinoma (Microinvasive Carcinoma or Invasive Carcinoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main duct type or combined type</td>
<td>≥15</td>
<td>0/1</td>
<td>1/1 (100)</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td></td>
<td>&lt;15</td>
<td>3/5 (60)</td>
<td>1/3 (33)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>Branch duct type</td>
<td>≥30</td>
<td>0/1</td>
<td>0/2</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>0/4</td>
<td>0/3</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

Table 4. Histologic Stage According to the Presence of Mural Nodules

<table>
<thead>
<tr>
<th>Mural Nodules</th>
<th>No. of Tumors With Nodules/No. of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Forms</td>
<td>Benign Forms</td>
</tr>
<tr>
<td>Mural nodules</td>
<td>21 (64)</td>
</tr>
<tr>
<td>No mural nodules</td>
<td>12 (36)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (100)</td>
</tr>
</tbody>
</table>
malignancy. For branch duct type, contrary to the findings of the Sugiyama and Atomi study, there was no correlation between the size of cystic duct dilation and malignancy.2

Tumors with mural nodules have a significantly higher incidence of carcinoma than tumors without nodules.2,14 In accordance with our results showing more cases of the malignant form (P < .006) and of invasive carcinoma (P < .001) in patients with mural nodules. The degree of papilla formation may range from microscopic folds to florid branching papillary nodules (up to several centimeters) with 2 different patterns of papillae, i.e., intestinal type (85%) and pancreaticobiliary type (15%).20 Mural nodules 3 mm or larger within the dilated main or branch pancreatic ducts can be detected in 53% to 64% of cases.2,18 In our series, they were found in 49% of cases. The positive predictive value for the malignant form is 81% of cases with mural nodules, and the latter were associated with a malignant form and invasive carcinoma, in accordance with previous results.2

We believe that it is more important to associate the criterion of size with the presence of mural nodules. Indeed, in Sugiyama and Atomi’s series, the 2 patients with a carcinoma and a diameter of the tumor less than 30 mm had mural nodules.2 In accordance with these authors, we did not find any carcinoma in branch duct types when the lesion diameter was less than 30 mm if patients did not have mural nodules. In our branch duct-type group, 2 patients had carcinoma and lesions smaller than 30 mm, but they had mural nodules. However, the results are different with the diameter of the main pancreatic duct in patients with main duct type and combined pancreatic duct type. We had 3 noninvasive carcinomas and 2 invasive carcinomas without mural nodules when the main pancreatic duct was less than 15 mm. As a result, the presence of mural nodules plays a crucial role in determining surgical strategy, especially in small branch duct tumors. This problem illustrates the significance of radiologic examinations for surgical strategy.

Endoscopic ultrasonography and magnetic resonance cholangiopancreatography (MRCP) were better than endoscopic retrograde cholangiopancreatography (ERCP) for observing the location of the tumor and the presence of mural nodules.2,9 Nevertheless, ERCP could help to predict malignancy with analysis of bile juice, as in the Tateishi et al21 series. In that study, the K-ras mutation was found in 9 of 15 patients with IPMT vs 1 of 27 patients without carcinoma21; however, this type of analysis remains controversial.3 Both MRCP and endoscopic ultrasonography can find signs of invasion in the case of invasive carcinoma but are not able to distinguish between intraductal carcinomas and benign lesions.2 Sugiyama and Atomi2 reserved ERCP for examining patients with equivocal MRCP findings, because MRCP is less operator-dependent and less invasive than ERCP. Recently, intraductal ultrasonography with a 2.5-mm-diameter miniature ultrasonographic probe was used to locate the tumor and the mural nodules and to perform biopsies,22 but this method of performing biopsies is exposed to inaccuracies because of varying degrees of epithelial dysplasia in different parts of the ductal system.

Surgical treatment is mandatory because of the frequency of malignant forms9,13,15,23-25 and because of the subsequent mortality due to invasive carcinoma.9,10 Frozen section of the pancreatic margin is one of the guidelines of the adequacy of the pancreatic resection.3,24,26,27 Cuillerier et al33 used it in cases of noninvasive carcinoma to extend pancreatic resection until disease-free margins are obtained. Operative ultrasonography can help to show local invasion, mural nodules, and lymph node involvement.14 The diagnosis sensitivity seems to be better with a high-resolution annular array transducer than with conventional operative ultrasonography.7

Multiple locations are possible,7,9,10,25,26 and Kobari et al34 suggested performing a total pancreatectomy routinely in the main duct type. In contrast, Cuillerier et al33 consider that total pancreatectomy should be performed only in highly selected patients, according to the general condition and age, even in the case of invasive carcinoma. Most authors choose to perform operations that preserve as much pancreatic tissue as possible when surgery is performed at an early stage of the disease.10,14,18,26,28 These operations include pylorus-preserving head pancreatectomy, duodenum-preserving pancreatic head resections with direct anastomosis between the remnant pancreas and the duodenum,17,23,29 pancreatic head resection with segmental duodenectomy,30 inferior head resection of the pancreas,31 segmental resection for tumors localized in the body,10,32 or enucleoresection.32 In this last type of resection, the patients must have routine examination during the postoperative follow-up mainly by MRCP, which can be associated with endoscopic ultrasonography. Indeed, in the series by the French Association of Surgery, 1 of the 2 patients who underwent enucleoresection presented with a recurrence that required a distal pancreatectomy 2 years after the initial surgery.12

Takeyoshi et al34 performed middle pancreatectomy and local lymph node resection in one patient with body lesions of less than 30 mm at intraoperative ultrasonography and with negative frozen sections of the pancreatic margin, although the final diagnosis was carcinoma. Even though the patient was still alive after 33 months, this limited resection may not be curative. Our group previously described a patient whose frozen sections of the pancreatic margins were negative after middle pancreatectomy, but who had an invasive carcinoma with 2 positive satellite lymph nodes.32

Finally, limited resection is possible in highly selected patients who fulfill the following criteria: branch duct tumor less than 30 mm and absence of mural nodules at preoperative and intraoperative examinations. In only these specific patients, limited resection such as middle pancreatectomy for a tumor localized at the isthmus, or inferior head resection for a tumor localized in the uncinate process of the pancreas, can be adequate with a curative intent.

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