Clinicopathological Features of Malignant Intraductal Papillary Mucinous Tumors of the Pancreas

The Differential Diagnosis From Benign Entities

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Background: The accurate differential diagnosis of malignant intraductal papillary mucinous tumors (IPMTs) of the pancreas from benign IPMTs remains unclear.

Hypothesis: Predictive factors for differentiating malignant IPMTs from benign IPMTs can be documented.


Setting: Wakayama Medical University Hospital, Wakayama, Japan.

Patients: Twenty-seven consecutive patients with IPMTs (11 with adenoma, 3 with dysplasia, 5 with adenocarcinoma, and 8 with invasive adenocarcinoma) who underwent surgery were retrospectively analyzed in terms of clinicopathological features.

Main Outcome Measure: Clinical data, preoperative imaging findings, cytology, and tumor marker level, including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9), in serum and pure pancreatic juice.

Results: In preoperative imaging findings, the mean tumor size for the malignant IPMT group (81±18 mm) was significantly larger than that for the benign IPMT group (31±4 mm) \( (P=.002) \). The mean mural nodule size for the malignant IPMT group (9.8±4.4 mm) was significantly larger than that for the benign IPMT group (3.3±5.7 mm) \( (P=.002) \). The CEA levels in pure pancreatic juice in the malignant IPMT group (3051±7556 ng/mL) were significantly higher than in the benign IPMT group (41±80 ng/mL) \( (P=.003) \), although no significant differences in cytologic analyses and CA19-9 levels in pure pancreatic juice were found between the 2 groups.

Conclusion: Our findings suggest that tumor size larger than 30 mm, mural nodule size larger than 5 mm, and CEA levels higher than 110 ng/mL in pure pancreatic juice were predictive factors for diagnosis of malignant IPMTs.

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ELECTION OF A SURGICAL PROCEDURE FOR TREATING INTRADUCTAL PAPILLARY MUCINOUS TUMORS (IPMTS) still remains controversial, because IPMTs show a wide spectrum of histological characteristics, ranging from hyperplasia to invasive carcinoma.1-3 IPMTs are believed to have a favorable prognosis compared with ductal cell carcinoma.3-5 However, IPMTs have a poor prognosis when invasive carcinoma derived from IPMTs has developed.5-8 The biologic behavior of IPMTs remains unclear. Previous studies have been performed to differentiate malignant IPMTs from benign IPMTs by retrospective investigations of clinical data, imaging findings,1,9-15 cytologic analyses in pure pancreatic juice,16 or molecular analysis.17 Consequently, no consensus concerning early diagnosis of malignant IPMTs has been attained as yet. Moreover, a simultaneous analysis of these factors has not been performed, to our knowledge. We simultaneously retrospectively analyzed clinical data, imaging findings, cytologic analyses, and tumor markers in pure pancreatic juice. The aim of the present study was to determine preoperative factors that are predictive for the early diagnosis of malignant IPMTs.

METHODS

From January 1, 1999, to May 31, 2003, 27 patients with IPMTs were treated at Wakayama Medical University Hospital, Wakayama, Japan. Clinicopathologic data were reviewed to determine the age, sex, symptoms, and presence of other pancreatic disease. All patients underwent ultrasonography (US), computed tomography (CT), endoscopic US, and endoscopic retrograde pancreatography (ERP) for
preoperative imaging diagnosis. These imaging data were reviewed with respect to tumor location, tumor size, the largest diameter of the main pancreatic duct (MPD), and the presence of mural nodule. We retrospectively compared the preoperative imaging diagnostic data with histopathological findings to obtain sensitivity, specificity, and accuracy.

During ERP, brushing for cytologic analysis was performed, and then pancreatic juice was immediately collected for 10 minutes with a catheter inserted into the pancreatic duct after an intravenous injection of 50 U per body of secretin (Eisai Co Ltd, Tokyo, Japan). A sample was immediately put on ice and divided into 2 sections: one for cytologic examination and the other for measurement of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) levels. The cytologic samples of collected pancreatic juice were immediately put on ice after adding heparin. After pancreatic juice was centrifuged, the cell pellet was smeared on glass slides, fixed in 95% ethanol, and stained with the Papanicolaou technique. For measurement of CEA and CA19-9 levels, the pancreatic juice was centrifuged and the supernatants were measured with CEA or CA19-9 immunometric chemiluminescent assay kit (Bayer Medical Co, Tokyo, Japan) according to the manufacturer’s instructions. Serum levels of CEA and CA19-9 were also measured.

The resected pancreas specimens were fixed with 10% formaldehyde solution and serially cut into 5-mm intervals and embedded in paraffin. All tissue sections were stained with hematoxylin-eosin. Then all slides of the resected pancreas were reviewed by independent pathologists. Histologically, 14 patients had benign IPMTs (11 adenomas, including 2 MPD type, 5 branch duct type, and 4 combined type, and 3 dysplasias), and 13 patients had malignant IPMTs (5 adenocarcinomas, including 1 branch duct type and 4 combined type, and 8 invasive adenocarcinomas, including 2 MPD type and 6 combined type) according to the classification by Japan Pancreas Society.18 We retrospectively reviewed clinicopathologic and preoperative imaging diagnostic data to identify indicative signs of malignant IPMTs.

The optimal cutoff levels for tumor size, mural nodule size, and CEA in pure pancreatic juice for differentiation between benign and malignant IPMTs were sought by constructing receiver operating characteristic (ROC) curves, which were generated by calculating the sensitivities and specificities of tumor size, mural nodule size, and CEA data at several predetermined cutoff points.19 All values are expressed as mean±SD. The χ² test was performed to assess the difference in accuracy of imaging studies and to calculate differences in cases with and without mural nodule between benign and malignant IPMTs. All other statistical analyses were performed with the Mann-Whitney U test. Statistical significance was defined as P<.05.

RESULTS

CLINICAL CHARACTERISTICS

Clinical characteristics of the enrolled patients are given in Table 1. There were no significant differences in age, sex, and symptoms between the patients with benign and malignant IPMTs. Fourteen (52%) of 27 patients were asymptomatic. The reasons for performing imaging studies in asymptomatic patients were as follows: follow-up of other diseases, including diabetes mellitus, in 3 benign IPMT patients; annual medical examinations in 6 benign IPMT patients; other diseases in 4 malignant IPMT patients; and annual medical examinations in 6 benign IPMT patients; other diseases in 4 malignant IPMT patients. The main symptom was pain in 11 (41%) of 27 patients. Only the malignant IPMT group experienced weight loss (15%). Twenty (74%) of 27 patients had no history of pancreatic disease. Seven (26%) of 27 patients had diabetes mellitus or chronic pancreatitis.

PREOPERATIVE IMAGING FINDINGS

The number of IPMTs located in the total pancreas was 4 (31%) of 13 in the malignant IPMT group and none in the benign IPMT group. Tumors were located in the pancreatic head in 6 patients in both the benign IPMT group and the malignant IPMT group and in the pancreatic body (tail) in 8 patients in the benign IPMT group and 3 in the malignant IPMT group. The dilatation of MPD measured by ERP was 7.8±6.5 mm in the benign IPMT group and 10.7±6.5 mm in the malignant IPMT group. There were no significant differences in location and dilatation of MPD between the benign and malignant IPMT groups. However, the mean tumor size of 81±18 mm in the malignant IPMT group was significantly larger than that of 31±4 mm in the benign IPMT group (P=.002). The mural nodules were present in 6 patients with benign IPMTs and 12 patients with malignant IPMTs. There was a significant difference between the benign IPMT group and the malignant IPMT group related to the presence of mural nodule (P=.007). In addition, the mean mural nodule size of 9.8±4.4 mm in the malignant IPMT group was significantly larger than that of 3.3±5.7 mm in the benign IPMT group (P=.002). Sensitivity, specificity, and accuracy for differentiating benign from malignant IPMTs were 75%, 50%, and 62% by US; 92%, 85%, and 89% by CT; 91%, 64%, and 78% by endoscopic US; and 91%, 57%, and 73% by ERP, respectively. The accuracy rate by CT was higher than that of US (P=.009).

CYTOLOGIC ANALYSIS

OF PURE PANCREATIC JUICE

Brushing for cytologic analysis was performed. A total of 20 mL of pure pancreatic juice was collected in 23 patients by intravenous injection of secretin. The cyto-

Table 1. Clinical Characteristics of 27 Patients With Intraductal Papillary Mucinous Tumors (IPMTs) of the Pancreas

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign IPMT Group (n = 14)</th>
<th>Malignant IPMT Group (n = 13)</th>
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<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>65 ± 3</td>
<td>72 ± 1</td>
</tr>
<tr>
<td>Sex ratio, M:F</td>
<td>1.3:1</td>
<td>1.7:1</td>
</tr>
<tr>
<td>Symptoms, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>9 (64)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (36)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Pancreatic disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (79)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (7)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>2 (14)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>
logic specimen of pure pancreatic juice after brushing could be examined in 11 patients in the benign IPMT group and 12 patients in malignant IPMT group (Table 2). In the remaining 4 patients, deep cannulation for brushing for cytologic examination could not be performed or a sufficient amount of sample of pure pancreatic juice could not be collected for cytologic analysis. Two (17%) of 12 patients with malignant IPMTs were diagnosed as having a malignancy (class IV or V), and 10 (91%) of 11 patients with benign IPMTs were diagnosed as having benign disease (class I, II, or III). One patient diagnosed as having a cytologic malignancy in the benign IPMT group had histologic dysplasia and premalignant lesions.

**TUMOR MARKERS IN PURE PANCREATIC JUICE AND SERUM**

Both CEA and CA19-9 levels in pancreatic juice could be measured in 11 patients in the benign IPMT group and 9 patients in the malignant IPMT group. In the other 7 patients, a sufficient amount of supernatant could not be collected after the centrifugation of pancreatic juice. Serum CEA and CA19-9 levels could also be measured in all patients. Carcinoembryonic antigen levels in pancreatic juice in the malignant IPMT group (3051 ± 7556 ng/mL) were significantly higher than those (41 ± 80 ng/mL) in the benign IPMT group (P = .003). However, we found no significant differences between the benign and malignant IPMT groups in serum CEA levels (1.8 ± 1.2 ng/mL vs 3.0 ± 2.4 ng/mL), CA19-9 levels in pancreatic juice (412 ± 416 ng/mL vs 9630 ± 13511 ng/mL), and serum CA19-9 levels (18 ± 35 ng/mL vs 262 ± 777 ng/mL).

**PREDICTIVE FACTORS FOR MALIGNANT IPMT DIAGNOSIS**

This study clarified that predictive factors for differentiating benign IPMTs from malignant IPMTs were tumor size, mural nodule size, and CEA levels in pure pancreatic juice. The ROC curves for tumor size, mural nodule size, and CEA levels of pure pancreatic juice are presented in Figure 1. With regard to the tumor size and mural nodule size by preoperative imaging findings, diagnostic cutoff levels for differentiation between benign IPMTs from malignant IPMTs were 30 and 5 mm, respectively (Figure 2). The sensitivities of the cutoff line in tumor size and mural nodule were 92% and 85%, respectively, and the specificity of the cutoff line was 71% for both. Therefore, the accuracies were 81% and 81%, respectively. The cutoff level of CEA in pure pancreatic juice was at 110 ng/mL for differentiation between benign and malignant IPMTs (Figure 3). The sensitivity of the CEA cutoff line was 78%, the specificity was 91%, and the accuracy was 80%.

**COMMENT**

The early diagnosis of malignant IPMTs is important for improving prognosis. Invasive carcinoma derived from IPMTs has been reported to be the most important factor that influences survival in patients with IPMTs and

<table>
<thead>
<tr>
<th>Class</th>
<th>Benign IPMT Group (n = 11)</th>
<th>Malignant IPMT Group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
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<td>IV</td>
<td>1</td>
<td>1</td>
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<td>V</td>
<td>0</td>
<td>1</td>
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</table>

Table 2. Comparison of Cytologic Analyses of Pure Pancreatic Juice Between Benign and Malignant Intraductal Papillary Mucinous Tumor (IPMT) Groups

Figure 1. Receiver operating characteristic curve of tumor size (A), mural nodule size (B), and carcinoembryonic antigen level of pure pancreatic juice (C) for estimation of a cutoff level differentiating malignant from benign intraductal papillary mucinous tumors.

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predicts a low survival compared with noninvasive carcinoma.5,20-23 In particular, prognosis in invasive carcinoma was reported to be influenced mainly by the extrapancreatic tumor extension or lymph node metastasis.5,22 It is important to differentiate malignant from benign IPMTs before IPMTs invade the extrapancreatic tissue. However, differentiating malignant from benign IPMTs preoperatively using only a single diagnostic method is still difficult despite significant improvement in imaging techniques. Indeed, in this study, preoperative CT diagnosis had a higher accuracy rate than US; however, controversy still exists regarding which imaging modality is best for preoperative diagnosis.

In the present study, we simultaneously analyzed clinicopathological features, imaging findings, cytologic analysis results, and tumor markers (CEA and CA19-9) in pure pancreatic juice to evaluate the characteristics of invasive carcinoma derived from IPMTs. We clarified predictive factors for preoperative diagnosis of malignant IPMTs. Previous studies have shown that tumor size, the size of mural nodule, or the dilatation of MPD were important factors in diagnosing malignant IPMTs.24-26 Although tumor size and mural nodule size are not uniform according to investigators, and no consensus concerning the early diagnosis of malignant IPMTs has been attained as yet,9,13 we propose that tumors larger than 30 mm and mural nodules larger than 5 mm as determined by imaging findings indicate a strong possibility of malignancy. According to preoperative imaging diagnosis, one should select function-preserving procedures for benign IPMTs, and intraoperative frozen section of the cut end of the pancreas should provide the adequate pancreatic resection.

Although cytologic examination of pure pancreatic juice or detection of K-ras mutation has previously indicated the diagnosis of malignant IPMTs,14,15,27-29 the accuracy was generally reported to be limited, and the diagnosis of malignant IPMTs is difficult using only a single method. In our study, the sensitivity of cytologic examination was low (17%) and indicated that it is difficult to differentiate malignant IPMTs only by cytologic examination of pure pancreatic juice. Some previous studies10-32 reported that the CEA level in pancreatic juice in pancreatic cancer was significantly higher than that in benign pancreatic disease. However, the measurement of CEA and CA19-9 levels in pure pancreatic juice has not been performed for differentiation of malignant and benign IPMTs. We compare benign with malignant IPMTs for the first time, to our knowledge, by measurement of CEA and CA19-9 levels of pure pancreatic juice. The CEA levels in pancreatic juice in the malignant IPMT group were significantly higher than those in the benign IPMT group. In this study, we propose that the introduction of a cutoff value for CEA level (110 ng/mL) in pure pancreatic juice allowed most of the false-positive results for benign IPMTs to be ruled out. The measurement of CEA levels in pure pancreatic juice was strongly suggested to be a useful diagnostic method to differentiate malignant from benign IPMTs. In this study, we had incidents of high CEA levels in pure pancreatic juice in the benign IPMT group. The cases were histologically severe atypia with premalignant lesions, which indicates a high potential for CEA production.2 On the other hand, with regard to the incidents of low CEA levels in the malignant IPMT group, there was a possibility that the collection of pure pancreatic juice was not appropriate for stenosis of the MPD by invasive carcinoma. It has been reported that the immunohistochemical staining of CEA is strongly positive in the cytoplasm of the tumor cells in the invasive IPMTs22 and shows a relation to the cellular atypia grade of IPMTs.2 Therefore, CEA may much more easily migrate to pancreatic juice than serum, and CEA levels in pure pancreatic juice may be much higher in malignant IPMTs than in benign IPMTs even if CEA levels in serum may be normal.

Future studies using immunohistochemical staining for CEA should be performed to clarify the correlation between pancreatic juice CEA and expression of CEA in IPMT cells. We must determine preoperative factors that are predictive for the accuracy of diagnosis of malignant IPMTs. In our study, tumor size larger than 30 mm, mural nodule size larger than 5 mm, and CEA levels higher than 110 ng/mL in pure pancreatic juice were predicted as predictive factors for diagnosis of malignant IPMTs. Further studies in larger series of patients with IPMTs are necessary to confirm the data presented herein.

Figure 2. The distribution of tumor size (A) and mural nodule size (B) in the benign intraductal papillary mucinous tumor (IPMT) group (n = 14) and the malignant IPMT group (n = 13). The cutoff levels of tumor size and mural nodule size are 30 and 5 mm, respectively.

Figure 3. The distribution of carcinoembryonic antigen (CEA) level in pure pancreatic juice in the benign intraductal papillary mucinous tumor (IPMT) group (n = 11) and the malignant IPMT group (n = 9). The cutoff CEA level in pure pancreatic juice is 110 ng/mL..
REFERENCES


