Pancreatic Ductal Adenocarcinomas in Long-Term Follow-Up Patients With Branch Duct Intraductal Papillary Mucinous Neoplasms

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Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary-mucinous neoplasms

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Running Title: Pancreatic cancers in patients with branch duct IPMNs

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Abbreviations: intraductal papillary-mucinous neoplasm (IPMN), pancreatic ductal adenocarcinoma (PDA), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), computed tomography (CT), standardized incidence ratio (SIR)

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Abstract

Objective: Although branch duct intraductal papillary-mucinous neoplasms (BD-IPMNs) are slow-growing tumors with a favorable prognosis, the synchronous occurrence of pancreatic ductal adenocarcinomas (PDAs) in patients with BD-IPMNs has been reported. This study aims to elucidate the development of PDAs in long-term follow-up patients with BD-IPMNs.

Methods: We investigated 89 BD-IPMN patients who had no mural nodules and were followed conservatively at least two years (median follow-up 64 months; range 25-158). All subjects underwent examinations by imaging modalities including endoscopic retrograde pancreatography. We calculated the standardized incidence ratio (SIR) from the vital statistics compiled by the Ministry of Health, Labor and Welfare of Japan.

Results: Among the 89 patients, four cases of PDAs distant from BD-IPMN were observed in 552 patient-years of follow-up (7.2 per 1,000 patient-years). The expected number was 0.25, and the SIR of PDAs was 15.8 (95% CI 4.3-40.4; p=0.00014). Subgroup analyses showed that the incidence of PDAs was significantly increased in patients ≥70 years (SIR 16.7; 95% CI 3.4-48.7; p=0.0008) and in females (SIR 22.5; 95% CI 2.7-81.1; p=0.0037).

Conclusions: Patients with BD-IPMNs are at a high risk for PDAs. During the follow-up, careful examination is required to detect the development of PDAs in patients with BD-IPMNs.

Key Words: IPMN; branch duct; pancreatic cancer; risk factor; follow-up.
Introduction

Intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas are characterized as intraductal papillary growths of neoplastic, mucin-producing columnar cells that arise in the main pancreatic duct or its major branches. IPMNs can be subdivided into main duct (MD-IPMN) and branch duct (BD-IPMN) types depending on whether the lesion is located in the main pancreatic duct or the side branch. Various reports have demonstrated that there are significant differences in the presence of cancer between MD-IPMN and BD-IPMN, ranging from 57% to 95% and 6% to 46%, respectively. The largest series on patients with MD-IPMNs showed that approximately 70% are symptomatic, 60% had carcinoma and 46% had invasive carcinoma. In contrast, the risk of malignancy in BD-IPMNs, in which patients have neither symptoms nor a mural nodule, and a cyst size <30 mm, is much lower than in the case of MD-IPMNs. Thus, BD-IPMNs are less aggressive compared with MD-IPMNs, and the classification of IPMNs has substantial value in determining the management strategy for this neoplasm.

The majority of IPMNs are BD-IPMNs, which are being diagnosed with increasing frequency as a result of recent improvement in imaging modalities and increasing clinicians’ awareness. BD-IPMNs are histologically distinct from pancreatic ductal adenocarcinomas (PDAs) and are associated with a better prognosis than PDAs which are a highly lethal malignancy. Although the outcome for BD-IPMNs is generally good, PDAs are sometimes found distant from a BD-IPMN in about 3.3% to 9.2% of cases. Conversely, small BD-IPMNs have been detected incidentally in pancreata resected for PDAs. There have also been reports of PDAs developing in the remnant pancreas several years after the resection of BD-IPMN. Consequently, these reports raise the question of whether a pancreas with BD-IPMNs may be at high risk for additional pancreatic cancer. In our present study, we aimed to investigate the development of PDAs in BD-IPMN patients who were followed conservatively.

Patients and Methods

Definitions

BD-IPMNs were diagnosed based on the pathognomonic findings of endoscopic retrograde pancreatography (ERP), i.e., a dilated cyst greater than 10 mm in size, communication between the cyst and the main pancreatic duct (MPD), and the presence of mucin, as indicated by filling defects in the pancreatic duct; this diagnosis was confirmed by ERP in all cases at diagnosis of BD-IPMNs. To exclude mucinous cystic tumors of the pancreas or pseudocysts, characteristic findings of imaging studies, such as a grape-like multilocular cystic lesion communicating with the MPD, were confirmed by computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS) in all cases. The maximum diameter of the dilated branch duct was measured by EUS and MRCP. Mural nodules in dilated branch ducts were diagnosed by MRCP and CT. Multifocal BD-IPMN was diagnosed via images that showed the synchronous presence of more than one BD-IPMN lesion, each occurring in distant anatomical area of the pancreas.

The diagnosis of pancreatic ductal adenocarcinoma (PDA) had to be confirmed by histological examination using endoscopic ultrasonography fine needle aspiration biopsy (EUS-FNA), endoscopic pancreatic biopsy, or surgical resection.

Patients and Follow-up

Between 1990 and December 2007, 89 patients with BD-IPMN (56 men, median age 74 years) who had
no mural nodules and fulfilled the diagnostic criteria of BD-IPMN listed above were included in the study. Of 89 patients, 82 were included in our previous study. They were followed as outpatients once or twice a year for more than two years. Abdominal imaging modalities including EUS in combination with CT and/or MRCP were performed once or twice a year. Serial changes of the pancreas, including the BD-IPMN lesions, were studied during the observation periods which ranged from 25 to 158 months (median follow-up 64 months). There was no available information on smoking, an established risk factor for PDA.

**Data Collection and Statistical Analysis**

We used age-stratified and sex-specific data on the incidence of cancer in Japan, as provided by the Japanese Journal of Health and Welfare Statistics in 2007, to determine the expected number of cases of PDAs in the follow-up series. Patient-years (that is, the observation time for one patient followed for one year) were calculated starting from the date of clinical diagnosis of BD-IPMNs and ending at either the end point of the study or on the date a PDA was diagnosed. The cumulative incidence of the development of PDAs apart from BD-IPMNs was analyzed by the Kaplan-Meier method. The ratio of the number of observed cases of PDAs in the BD-IPMN patients who were followed to the expected number of cases (standardized incidence ratio (SIR)) was used to estimate the relative risk. The 95% confidence interval (CI) for the SIR was calculated assuming that the observed cases of PDAs followed a Poisson distribution.

Statistical significance was analyzed using the Fisher exact chi-square test. Differences were considered to be significant when the *p*-value was less than 0.05. All of the statistical tests were two-tailed.

**Results**

Characteristics of the 89 follow-up patients with BD-IPMNs

Characteristics of the 89 BD-IPMN patients with a follow-up period of more than 2 years are summarized in Table 1. They consisted of 56 men and 33 women, with a median age of 74 years (range, 42-88 years). The median follow-up duration was 64 months (range, 25-158 months). Overall, the BD-IPMN lesion was located either in the head or in the body to tail of the pancreas in 32 (36.0%) and 40 (44.9%) of the 89 patients, respectively. The median size of the BD-IPMN was 20 mm (range, 11-65 mm). Twenty-two (24.7%) of the 89 patients had a dilated branch duct diameter >30 mm. Four (4.5%) BD-IPMNs had newly developed mural nodules. Although one patient (1.1%) had recurrent pancreatitis, the remaining patients were asymptomatic. After a median follow-up of 78 months (range, 25-154 months), surgical resections of the BD-IPMN lesions were carried out in 10 cases with newly developed (n=4) mural nodules, cystic enlargement (n=5), or recurrent pancreatitis (n=1).

**Development of PDAs in patients with BD-IPMNs during follow-up**

After a follow-up period with a median of 63 months (range, 37-92 months), four PDAs (4.5%) metachronously developed in the pancreata apart from the BD-IPMN (Table 2). There were no cases with developing of cancer within the BD-IPMN. The patients who developed the PDAs included two men and two women of a median age 72 years (range, 66-75 years) at the time of diagnosis of the PDAs. None of the four cases with PDAs had symptoms, mural nodules, or a cyst size >30 mm. The median cyst size in the cases with PDAs was not significantly different from the cases without PDAs (*p*=0.55). In these four patients, yearly plain CT and EUS was performed. Three of four patients with PDAs had high levels of serum CA19-9 at the diagnosis.
of PDAs. One of these four patients underwent surgical resection, and the remaining three received systemic chemotherapy with gemcitabine.

Remaining 75 asymptomatic patients without mural nodules and cystic enlargement, including 17 (22.7%) with a cyst size >30 mm, continued to be followed conservatively, with a median follow-up of 64 months (range, 25-158 months) (Table 1).

**Risk of PDAs in follow-up patients with BD-IPMN**

During the follow-up period of more than two years, four PDAs (4.5%) distant from the BD-IPMN in the same pancreas were observed in 552 patient-years of follow-up (7.2 per 1,000 patient-years). All four patients died from the PDAs. When compared with the expected mortality rates based on the vital statistics of Japan, the expected number of PDAs among patients with BD-IPMN who are ≥40 years of age was 0.25, yielding an SIR of 15.8 (95% confidence interval (CI) 4.3-40.4; p=0.00014) (Table 3). Subgroup analyses showed that the incidence of PDAs was significantly increased in those ≥70 years of age (SIR 16.7; 95% CI 3.4-48.7; p=0.0008) and in females (SIR 22.5; 95% CI 2.7-81.1; p=0.0037). The cumulative incidence of PDAs analyzed by the Kaplan-Meier method was 3.0% at 5 years and 8.8% at 10 years (Figure 1).

**Discussion**

Recent reports and consensus guidelines for IPMN show that BD-IPMNs are less aggressive compared with MD-IPMNs, and suggest that BD-IPMNs that cause no symptoms and have a cyst size <30 mm and no mural nodules can be followed-up with periodic imaging examinations. These reports would increase the nonsurgical management for BD-IPMN patients who fail to meet certain high-risk criteria, which are indicated by consensus guidelines for the management of IPMNs.

This study suggests that the risk of developing PDA is increased in BD-IPMN patients as compared to age- and sex-matched controls (SIR 15.8; 95% CI 4.3-40.4; p=0.00014). Identifying clinical characteristics that identify BD-IPMN patients who are at high risk for PDA would help enrich the pool of newly diagnosed or follow-up BD-IPMN patients. In this respect, Tada et al. reported a follow-up study in which PDAs developed in five of the 197 patients with cystic lesions of the pancreas including 80 BD-IPMN patients; a significant difference was found only in age, but not in gender, or cyst location and size between the patients who developed PDAs and those who did not. In our study, the incidence of PDAs was significantly increased in patients of age ≥70 years (SIR 16.7; 95% CI 3.4-48.7; p=0.0008) and in females (SIR 22.5; 95% CI 2.7-81.1; p=0.0037). Uehara et al. also reported that BD-IPMN patients over 70 years old developed ductal carcinoma significantly more frequently than those under 69. However, we found no significant differences in cyst size and location between patients with and without PDAs. Interestingly, none of the four BD-IPMN patients with PDAs had symptoms, mural nodules, or a cyst size >30 mm, as is necessary to indicate resection in consonance with criteria described by the international consensus guideline. In contrast, these resection criteria were frequently met in 22 (25.9%) of 85 cases without PDAs after follow-up. These results suggest that special attention should be paid to the BD-IPMN patients who are age 70 years or older and female, and that the recent consensus guideline for resection is likely unable to identify a high risk BD-IPMN patient for PDA.

In the international consensus guidelines for IPMN, it is indicated that the interval of follow-up can be lengthened after two years of no change. However, the results of this study showed that the interval should not be lengthened even if a change will not be seen in two years.
or more. This study emphasizes the importance of long-term careful surveillance of the entire pancreas in patients with BD-IPMN. Belyaev et al. performed Medline-based systemic review of the published data including 3,725 patients with IPMN, and reported that surveillance policy requires attention to the entire pancreas to detect eventual development of concomitant PDA 17. A treatment algorithm of BD-IPMN is demonstrated in Figure 2, in which we propose that long-term surveillance is required for detection of PDA in patients with BD-IPMN. Since yearly plain CT and EUS was performed in four patients with PDA, we could not detect PDA at an early stage. Therefore, half-a-year follow-up with contrast-enhanced CT and EUS may be recommended to detect development of PDA earlier, as well as to changes within the BD-IPMN. The diagnostic value of half-a-year imaging studies, such as contrast-enhanced CT and EUS, should be evaluated prospectively during follow-up of asymptomatic Br-IPMN patients in order to detect PDA at a potentially curable stage.

Although the mechanisms underlying the risk of PDA in BD-IPMN patients are unclear, evidence suggests that the presence of pancreatic intraepithelial neoplasia (PanIN) lesions may play an important role in the development of PDA within a pancreas harboring BD-IPMN 31-33. Notably, PanIN lesions, which are morphologically distinct from IPMN and thought to be the putative precursors of PDA, are found with high frequency in the ducts of resected pancreata harboring IPMNs 33-35. In addition, PanIN lesions that are more dysplastic than the coincident IPMN are detected in the ducts distant from the IPMN, indicating that the development of a PDA may be the result of the progression of PanIN lesions in a pancreas harboring BD-IPMN.

On the other hand, one of the important clinicopathologic features of IPMN is tumor multifocality, ranging from 9.8% to 32% 14, 36-38. A study of IPMN treated with a total pancreatectomy showed multifocal discontinuous sites of dysplasia within the pancreatic ducts 39. These observations support the hypothesis that a field defect that causes multiple primary neoplastic lesions exists in pancreata harboring IPMN 31. In this study, we found 17 (19.1%) multifocal BD-IPMNs in 89 patients, which is consistent with a recent study reported by Rodriguez et al. wherein 21 (14.5%) of 145 BD-IPMN were multifocal 14. However, none of the four PDAs had a multifocal occurrence of BD-IPMN, and there was no development of PDA in the 17 cases with multifocal BD-IPMN. Our data suggest that the development of PDA may have a different pathogenesis from the occurrence of multifocal BD-IPMN.

Another explanation behind the development of PDAs in a pancreas harboring BD-IPMN is that K-ras aberrations occur early in the development of PanIN lesions identified in the ducts that are distant from the IPMN 31, 32. Activating K-ras mutations are detected in nearly 90% of PDAs. In a mouse model with an endogenous K-ras mutation, the full spectrum of human pancreatic carcinogenesis was recapitulated with murine PanIN lesions progressing to PDA 40. A recent report using a mouse model demonstrated that concomitant pancreatic activation of K-ras and transforming growth factor alpha results in PanIN lesions and cystic papillary neoplasms reminiscent of human IPMN and that these lesions progress to invasive cancer 41. These animal studies which focus on the progression of K-ras-initiated neoplasms could provide insight into a mechanism underlying the risk of PDA in a pancreas harboring BD-IPMN in humans.

In conclusion, our study suggests that patients with BD-IPMNs are at a high risk for PDAs. During the follow-up, careful examination is required to detect the development of PDAs in patients with BD-IPMNs.
REFERENCES


34. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and


**Figure Legends**

**Figure 1.** Cumulative incidence of developing PDAs in follow-up patients with BD-IPMNs. The cumulative incidence of PDAs analyzed by the Kaplan-Meier method was 3.0% at 5 years and 8.8% at 10 years.

**Figure 2.** Algorithm for the treatment of BD-IPMN. Interval of follow-up should not be lengthened even if a change will not be seen in two years or more. Half-a-year follow-up with contrast-enhanced CT and EUS may be recommended to detect development of PDA earlier, as well as to changes within the BD-IPMN.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=89)</th>
<th>Development of PDAs (n=4)</th>
<th>Surgery for BD-IPMN (n=10)</th>
<th>Continued follow-up (n=75)</th>
</tr>
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<tbody>
<tr>
<td>Median age (y) (range)</td>
<td>74 (42-88)</td>
<td>72 (66-75)</td>
<td>72 (42-81)</td>
<td>74 (44-88)</td>
</tr>
<tr>
<td>Male (N) (%)</td>
<td>56 (62.9%)</td>
<td>2 (50%)</td>
<td>7 (70%)</td>
<td>47 (62.7%)</td>
</tr>
<tr>
<td>Location of BD-IPMN (N) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>32 (36.0%)</td>
<td>3 (75%)</td>
<td>3 (30%)</td>
<td>26 (34.7%)</td>
</tr>
<tr>
<td>Body-tail</td>
<td>40 (44.9%)</td>
<td>1 (25%)</td>
<td>4 (40%)</td>
<td>35 (46.7%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>17 (19.1%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
<td>14 (18.7%)</td>
</tr>
<tr>
<td>Median size of BD-IPMN (mm) (range)</td>
<td>20 (11-65)</td>
<td>19 (13-25)</td>
<td>31 (13-65)</td>
<td>17 (11-45)</td>
</tr>
<tr>
<td>Median duration of follow-up (months) (range)</td>
<td>64 (25-158)</td>
<td>63 (37-92)</td>
<td>78 (25-154)</td>
<td>64 (25-158)</td>
</tr>
<tr>
<td>Indication for resection *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30 mm in size (N) (%)</td>
<td>22 (24.7%)</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
<td>17 (22.7%)</td>
</tr>
<tr>
<td>Mural nodule (N) (%)</td>
<td>4 (4.5%)</td>
<td>0 (0%)</td>
<td>4 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Symptomatic (N) (%)</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Indication for resection according to IPMN guideline
### Table 2  Characteristics of the patients who developed PDAs that were distant from BD-IPMN in the pancreas

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y) / Sex</th>
<th>BD-IPMN</th>
<th>Duration of follow-up (months)</th>
<th>PDA</th>
<th>Diagnostic procedure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73 / F</td>
<td>Head</td>
<td>25</td>
<td>Body</td>
<td>25</td>
<td>466</td>
</tr>
<tr>
<td>2</td>
<td>75 / F</td>
<td>Head</td>
<td>22</td>
<td>Body</td>
<td>30</td>
<td>1,646</td>
</tr>
<tr>
<td>3</td>
<td>66 / M</td>
<td>Body</td>
<td>16</td>
<td>Tail</td>
<td>45</td>
<td>492</td>
</tr>
<tr>
<td>4</td>
<td>71 / M</td>
<td>Head</td>
<td>13</td>
<td>Tail</td>
<td>35</td>
<td>&lt; 3</td>
</tr>
</tbody>
</table>

\(^a\) Age at diagnosis of PDAs  
\(^b\) Endoscopic pancreatic biopsy  
\(^c\) Endoscopic ultrasonography-guided fine needle aspiration
Table 3  Observed and expected numbers of PDAs developed in 89 follow-up patients with BD-IPMN

<table>
<thead>
<tr>
<th>Groups</th>
<th>PDA (n)</th>
<th>Observed</th>
<th>Expected</th>
<th>Observed / expected ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (All subject)</td>
<td></td>
<td>4</td>
<td>0.25</td>
<td>15.8</td>
<td>4.3-40.4</td>
<td>p=0.00014</td>
</tr>
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<td>Stratified by age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 y</td>
<td></td>
<td>1</td>
<td>0.07</td>
<td>14.3</td>
<td>0.4-79.6</td>
<td>p=0.068</td>
</tr>
<tr>
<td>≥70 y</td>
<td></td>
<td>3</td>
<td>0.18</td>
<td>16.7</td>
<td>3.4-48.7</td>
<td>p=0.0008</td>
</tr>
<tr>
<td>Stratified by sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>2</td>
<td>0.18</td>
<td>10.9</td>
<td>1.3-39.4</td>
<td>p=0.0149</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>2</td>
<td>0.09</td>
<td>22.5</td>
<td>2.7-81.1</td>
<td>p=0.0037</td>
</tr>
</tbody>
</table>