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Progression of pancreatic branch duct-type intraductal papillary mucinous neoplasms (BD-IPMNs) after surgery for extrapancreatic malignancies

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Abstract

Background/aims The natural history of pancreatic branch duct-type intraductal papillary mucinous neoplasms (BD-IPMNs) is still unknown. This retrospective study aims to determine the morphological changes of BD-IPMNs with attention to the history of surgical resection for extrapancreatic malignancies.

Methods and materials This study included 427 subjects with BD-IPMN at the Osaka Medical College from January 2001 to December 2019; 134 patients were included. The predictive factors for the progression of BD-IPMN based on morphological changes were evaluated by univariate as well as multivariate analyses. Furthermore, the clinical features of BD-IPMNs with progressive lesions during follow-up were investigated.

Results The average interval of follow-up was 35.8 months (with a range between 12.1 and 157 months). Disease progression occurred in 6 subjects (4.5%). In two of them (1.5%), IPMN-related invasive carcinoma was found. Multivariate analysis demonstrated that surgical resection for extrapancreatic malignancies was a significant predictor of BD-IPMN progression.

Conclusion The history of resection of extrapancreatic malignancies should be considered during the follow-up of BD-IPMN.

Keywords Intraductal papillary mucinous neoplasm, Surgical stress, Branch duct type, Progression after surgery, Extrapancreatic malignancy

Introduction

Pancreatic intraductal papillary mucinous neoplasms (IPMNs) are characterized by papillary growth inside the pancreatic ductal system as well as increased mucin production. Besides, they are more prone to undergo a transformation of malignancy. Since their first description in 1982, IPMNs have been well characterized [1–4]. The natural history of branch duct-type IPMNs (BD-IPMNs) has been thoroughly researched; however, predicting malignancy remains difficult [5–10].

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One of the most significant characteristics of IPMN is that patients have an elevated risk of harboring extrapancreatic malignancies than patients with pancreatic ductal adenocarcinoma or other pancreatic cystic neoplasms or referred patients [11–15]. Thus, patients diagnosed with BD-IPMN often underwent surgical resection for extrapancreatic malignancies during follow-up. At that time, we sometimes had the impression that the IPMNs of the postsurgical patients progressed more aggressively than those of the normal follow-up patients. There were no studies that determined the true incidence of IPMN progression in individuals who had previously had surgical resection for extrapancreatic malignancies. Thus, in the present study, the natural history of IPMN, focusing on morphological changes with attention to a prior history of surgical resection for extrapancreatic malignancies, was evaluated.

Patients and methods

A total of 134 subjects with BD-IPMN were included in this study from January 2001 through December 2019 at the Osaka Medical College. In this retrospective study, our institute committees have given their approval.

To restrict the cases that the detailed condition was comprehended, the cases that endoscopic ultrasound (EUS) was not performed as the first examination were excluded. Also, the cases that the follow-up period was shorter than 1 year after the first EUS were excluded. Moreover, the medical history cases that included some extrapancreatic malignancies before the first diagnosis were excluded to evaluate the influence of newly appeared extrapancreatic malignancies solely.

BD-IPMN was defined based on the combination of images (EUS/magnetic resonance imaging (MRI)/computed tomography (CT)) as a disease characterized by a cystically dilated branch duct with documented ductal communication and with a main pancreatic duct (MPD) diameter of smaller than 10 mm. Fluid biochemistry, as well as EUS-fine-needle aspiration (FNA) cytology, was not used in the evaluation.

All EUS research was performed using a digital convex echoendoscope. Our hospital's three specialist endoscopists (A. I., T. O., and D. M.) evaluated the image findings. The dilated branch duct volume was estimated en bloc in multilocular cyst cases. According to the morphological characteristics on EUS, the absence or presence of mural nodules in cystic branches was evaluated. Multifocal cysts were classified as conditions with a distribution that involved two or more pancreatic sections. The cyst size of cases of multiple IPMNs was determined as that of the largest cyst. At least yearly imaging scans, including EUS, enhanced CT, and MRI, were part of the follow-up procedures.

Lesion progression has been defined as a 2-mm increase in the size of MPD, a 10-mm increase in the size of cyst, a 1-mm increase in the size of the mural nodule, or the presence of a pancreatic mass during follow-up screening.

Diabetes mellitus was defined as patients with a hemoglobin A1c (HbA1c) greater than 6.5% or cases administrated antidiabetic medications during BD-IPMN diagnosis.

Statistical analysis

Continuous variables were expressed as median values, whereas comparison of categorical parameters was performed utilizing Fisher's exact test, chi-squared test, and Mann–Whitney *U*-test, if applicable. Univariate as well as multivariate logistic regression analyses have been carried out to identify predictors of disease progression. *P*-values < 0.05 were considered significant.

Statistical analysis of data was performed via the 11th version of JMP software (SAS Institute Inc., Cary, NC, USA).

Results

Comparison of characteristics between follow-up patients with stable disease and those with disease progression

The characteristics for the 134 BD-IPMN patients are depicted in Table 1. The median duration of follow-up was 35.8 months (with a range of 12.1–157 months). Furthermore, there were 67 males as well as 67 females, with a median age reaching 68 years (range, 44–83 years). During follow-up, six patients were diagnosed with disease progression (4.5%, progression group), and 128 had no disease progression (95.5%, non-progression group).

The follow-up period of the progression group (18.4 months) was much shorter than that of the non-progression group (36.9 months, $P=0.0065$). No apparent differences have been detected in the prevalence of diabetes mellitus at the initial diagnosis, the rate of multifocal IPMN, the serum level of carcinoembryonic antigen (CEA), and carbohydrate antigen serum level (CA19-9) between the progression group as well as the non-progression group. During the first examination on EUS, the average diameter of the MPD was estimated to be 2.4 mm (range, 1.0–9.0) mm, and the median cyst size was 16 mm (range, 1.7–48.0 mm), which were similar in the two groups. Mural nodules were detected in 5 patients (3.7%) on the first EUS examination, all of which were in the non-progression group. Invasive carcinoma derived from IPMN was seen in 2 cases (33.3%) in the progression group, much more than in the non-progression group ($P<0.0001$). Five patients underwent surgery for IPMN because of invasive carcinoma derived from IPMN ($n=2$, both progression group) and the patients' request even

Table 1 Characteristics of 134 cases of BD-IPMN as described in the clinical report

Factors	All patients *N* = 134	With progression of lesions *N* = 6	Without progression of lesions *N* = 128	*P*
Sex, male:female	67:67	3:3	64:64	1.00
Age, median (range), years	68 (44–83)	72 (59–80)	67.5 (44–83)	0.26
Diabetes mellitus at the initial diagnosis, *n* (%)	21 (15.7)	1 (16.7)	20 (15.6)	0.95
Follow-up period, median (range), months	35.8 (12.1–157)	18.4 (14.2–31.0)	36.9 (12.1–157)	**0.0065**
Number of multifocal IPMNs (multifocal/unifocal), *n* (%)	53 (39.6)	3 (50.0)	50 (39.1)	0.59
CEA, median (range), ng/ml	2.0 (0.2–11.2)	2.9 (1.5–7.2)	2.0 (0.2–11.2)	0.25
CA19-9, median (range), U/ml	10.3 (0.1–253.3)	16.0 (9.0–32.0)	9.85 (0.1–253.3)	0.12
Size of MPD at the initial diagnosis, median (range), mm	2.4 (1.0–9.0)	2.0 (1.2–6.0)	2.4 (1.0–9.0)	0.69
Size of cyst at the initial diagnosis, median (range), mm	16 (1.7–48.0)	22.5 (10.3–37.8	15.7 (1.7–48.0)	0.17
Presence of mural nodule at the initial diagnosis, *n* (%)	5 (3.7)	0	5 (3.9)	0.59
Invasive carcinoma derived from IPMN, *n* (%)	2 (1.5)	2 (33.3)	0	**< 0.0001**
Surgical resection of IPMN, *n* (%)	5 (3.7)	2 (33.3)	3 (2.3)	**< 0.0001**
Surgery for malignancy of other organs, *n* (%)	18 (13.4)	3 (50.0)	15 (11.7)	**0.0072**
Surgery for benign lesion of other organs, *n* (%)	7 (5.2)	0	7 (5.5)	0.56
Surgery for benign lesion of other organs, *n* (%)	5 (3.7)	0	5 (3.9)	0.62

BD-IPMN branch duct-type intraductal papillary mucinous neoplasm, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *MPD* main pancreatic duct

though they did not meet the progression criteria ($n = 3$, all non-progression group). The latter three patients had worrisome features based on the international consensus guidelines 2012 [16]. The percentage of surgical resection for malignancy of other organs was substantially elevated in the progression group (50.0%) compared to the non-progression group (11.7%, $P = 0.0072$). Extrapancreatic malignancies not treated surgically were seen in five cases, which were all included in the non-progression group (hepatocellular carcinoma in 2; both radiofrequency ablation, gastric cancer in 2, both endoscopic submucosal dissection, multiple myeloma in 1; best supportive care).

Predictors of lesion progression

Univariate and multivariate analyses of clinicopathological markers to determine the progression of IPMN revealed that only surgery for malignancy of other organs was a significant predictor (Table 2). On the contrary, surgery for a benign lesion of another organ was not a predictor.

Table 2 Analysis of factors predicting lesion progression

Factors	Univariate analysis			Multivariate analysis		
	OR	95% *CI*	*P*	*OR*	95% *CI*	*P*
Male	1.00	0.18–5.58	1.00			
Age	0.93	0.83–1.04	0.24			
Diabetes mellitus	1.08	0.05–7.18	0.95			
Multifocal cysts	1.56	0.28–8.72	0.59			
CEA value	0.81	0.58–1.2	0.26			
CA19-9 value	0.81	0.98–1.05	0.96			
Size of MPD	1.00	0.62–1.82	0.88			
Size of cyst	0.96	0.89–1.04	0.27			
Mural nodule (+)	0.96		0.49			
Surgery for malignancy of other organs	7.53	1.29–44.1	**0.0264**	8.73	1.14–76.8	**0.0379**
Surgery for benign lesion of other organs			0.42			

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *MPD* main pancreatic duct, *OR* odds ratio, *CI* confidence interval

Incidence and time of surgery for other organ malignancies

Among the total 134 patients, 18 underwent surgery for extrapancreatic malignancies after diagnosis of IPMN. The surgery was performed during IPMN diagnosis in 10 cases, most of which were detected by chance at the imaging examination for the surgery. Extrapancreatic malignancies of the remaining 8 cases were resected during IPMN follow-up. The most common extrapancreatic cancers after a diagnosis of IPMN were colorectal cancer (6 cases), lung cancer (2 cases), hepatocellular carcinoma (2 cases), endometrial carcinoma (2 cases), and breast cancer (2 cases) (Table 3).

Clinical features of patients with progressive lesions

The detailed clinical features of 6 patients who had progressive IPMNs are summarized in Table 3. The MPD was thickened in 3 cases (cases 1, 3, and 5), and the diameter of the cyst increased in all cases. Mural nodules appeared in 3 cases (cases 1, 3, and 6). Three of six (cases 2, 3, and 6) underwent surgery for other organ malignancies after diagnosis of IPMN. Two patients (cases 1 and 6) developed pancreatic cancer derived from IPMN; both are alive after curative surgery.

Discussion

Many studies have detailed the natural history of IPMN in order to differentiate between malignant as well as benign IPMN preoperatively. Salvia et al. demonstrated that only five of 89 BD-IPMN subjects underwent surgery because of an enlarging cystic lesion that was proven to be benign [5]. Tanno et al. observed 82 BD-IPMN patients without mural nodules [6]. They reported that four patients developed new mural nodules in a dilated branch duct, and, of these, only one developed malignancy. Ohno et al. showed that the presence of mural nodules at preliminary diagnosis as well as MPD involvement was significant predictors of malignant transformation of BD-IPMN on detailed examination based on morphological changes [7]. Shumit et al. reported that multivariate analysis of 103 cases demonstrated that atypical cytopathology and mural nodules were important indices of malignant BD-IPMN [8]. These studies examined many clinicopathological and imaging features to predict malignant alteration, but there is no consensus on which factor is related to the risk of malignancy.

Additionally, no studies investigated the history of surgery of other organs. In the present study, multivariate analysis showed that surgical resection for malignancy of other organs was the critical factor related to the progression of IPMN. This result was compatible with our impression from daily clinical practice. The stress of surgery for extrapancreatic malignancies may affect IPMN progression. Surgical procedures are stressful for our bodies, and a wide range of studies have demonstrated that the recurrence of neoplastic illness can take place postoperatively [17, 18]. Consequently, most data emphasize the importance of the perioperative interval in managing surgical cancers. Surgery induces inflammatory, neuroendocrine, metabolic, and immunological stress. In addition to upregulation of main malignant molecular pathways that contribute to tumorigenesis [19]. The findings of in vivo as well as in vitro studies demonstrated that the response of our body to surgical stress elevates the probability of metastatic cancer spread [20, 21]. In addition to surgical stress, anesthesia used in the surgery has also been found to affect cancer cell biology and its progression toward metastasis and invasion and increase immunosuppression in cancer patients undergoing surgery [21–23]. However, some studies have shown that the immunosuppressive condition associated with transplant surgery did not induce the progression of BD-IPMN [24, 25]; thus, a simple immunological deficiency state may not exacerbate BD-IPMN. Possible additional cancer-associated factors caused by surgical stress might have changed the environment around IPMNs. Interestingly, in the present study, IPMN was not exacerbated by surgery for benign disease represented by cholecystectomy for cholelithiasis, which was consistent with the above hypothesis. The presence itself of malignant disorders may have affected the progression of IPMN.

MPD diameter and the presence of nodules have been reported to be predictors of malignant IPMN in multiple studies [7–9]. MPD size and the existence of mural nodules on initial examination did not contribute to progression in the present study.

Table 3 Incidence and time of surgery for malignancies of other organs

	During follow-up of IPMN	Concurrent	Total
Colorectal cancer	3	3	6
Gastric cancer	1	0	1
Hepatocellular carcinoma	1	1	2
Ovarian cancer	0	1	1
Lung cancer	1	1	2
Prostate cancer	0	1	1
Endometrial cancer	1	1	2
Esophageal cancer	0	1	1
Breast cancer	1	1	2
	8	10	18

IPMN intraductal papillary mucinous neoplasm

Moreover, on initial examination, five patients with mural nodules were all included in the non-progression group. Sawai et al. concluded that MPD dilatation and the presence of mural nodules on the latest examination were predictors of malignancy. Still, no differences were seen in MPD size as well as mural nodules on preliminary examination between the benign group and the malignant group [9]. Among six patients who developed pancreatic cancers during follow-up, only one had a mural nodule during the preliminary diagnosis. Furthermore, Kobayashi et al. illustrated that the height of mural nodules, the average MPD diameter, and the presence of mural nodules on preliminary examination were not risk factors for pancreatic cancer with IPMN during follow-up [10]. The morphological features at the latest examination might be more important than those at the initial examination. A particular cut-off value should evaluate the presence of nodules; 3 to 10 mm has been suggested as a cut-off value for malignancy [26, 27], but no agreement has been achieved on the suitable cut-off value for the size of mural nodules.

EUS has the best resolution of the pancreas and has the potential to detect BD-IPMN morphological modifications, including serial changes in location and volume of MPD and mural nodules [7]. Hence, EUS is an effective tool in diagnosing and managing malignant cancers [28, 29]. Nodules appeared in three cases during follow-up in the present study, and two of these three cases were invasive carcinoma derived from IPMN. Fortunately, curative resection was possible in both cases. The reason for identifying these cases was that EUS was done regularly. Although EUS is more intrusive as well as operator dependent compared to CT/MRI, it is fundamental for assessing morphological modifications in mural nodule cases [7]. Periodic EUS combined with CT/MRI seems to be good management of BD-IPMN. Extrapancreatic malignancies were detected in 16.8 to 38% of patients with IPMN [11–15]. The majority were colorectal and gastric carcinomas. The present study shares some similarities and shows some differences from previous studies. In this research, 13.4% (18/134) of patients developed malignancies of other organs, and the majority were colorectal carcinoma ($n=6$). Because most IPMNs are asymptomatic, they are often found accidentally during examination for extrapancreatic cancer. In the present study, the number of IPMNs found with extrapancreatic malignancy simultaneously ($n=10$) was almost the same as the number of IPMNs found earlier than carcinoma of other organs ($n=8$). The cases that underwent surgery for malignant disorders of other organs before the diagnosis of IPMN were excluded in the present study. Thus, the effect of surgery history for past malignancies could not be examined, which is one of the limitations of this study. Since previous literature illustrated that cases harboring IPMNs are at elevated risk to develop a second malignancy concurrently or following being diagnosed with IPMN [30], attention should be paid to the appearance of extrapancreatic malignancies.

When interpreting the findings of this study, certain limitations must be acknowledged. First, because the extrapancreatic malignancies in BD-IPMN cases are uncommon, the current research study enrolled a small number of surgically resected subjects. Second, the design was done retrospectively using only data from a single tertiary center. Consequently, large-scale research is necessary to validate the factors associated with progression, particularly to determine the factors associated with malignant progression (just 2 cases in this study).

We conclude that conservatively managed BD-IPMN patients are associated with progression of the disease after surgical resection for extrapancreatic malignancies. A careful follow-up may be required when BD-IPMNs are discovered after resection of extrapancreatic tumors.

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Authors' contributions
All authors have substantially contributed to the conception and design, acquisition of the data, data analysis, and interpretation. All authors have agreed on the content of the manuscript. AI, TO, and DM, perform the EUS and evaluated the images; UA, KN, and TO, data collection, acquisition, and manuscript writing; YA, TT, TI, KI, and SN, study design, conception, statistical analysis, and manuscript revision; and KH, supervision of all steps of the study. The authors read and approved the final manuscript.

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Availability of data and materials
The data supporting the results are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the principles of the Declaration of Helsinki and was approved by Institutional Review Board (IRB) of Osaka Medical College, Osaka, Japan.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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