

# World Journal of *Clinical Oncology*

*World J Clin Oncol* 2019 February 24; 10(2): 28-109



**EDITORIAL**

- 28 Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide  
*Braga A, Mora P, de Melo AC, Nogueira-Rodrigues A, Amim-Junior J, Rezende-Filho J, Seckl MJ*

**MINIREVIEWS**

- 38 Oligometastases in prostate cancer: Ablative treatment  
*Palacios-Eito A, Béjar-Luque A, Rodríguez-Liñán M, García-Cabezas S*
- 52 Existing anti-angiogenic therapeutic strategies for patients with metastatic colorectal cancer progressing following first-line bevacizumab-based therapy  
*Kanat O, Ertas H*
- 62 Rational-emotive behavioral intervention helped patients with cancer and their caregivers to manage psychological distress and anxiety symptoms  
*Eseadi C*
- 67 Pancreatic cancer screening in patients with presumed branch-duct intraductal papillary mucinous neoplasms  
*Torisu Y, Takakura K, Kinoshita Y, Tomita Y, Nakano M, Saruta M*

**ORIGINAL ARTICLE****Retrospective Cohort Study**

- 75 Retrospective evaluation of FOLFIRI3 alone or in combination with bevacizumab or aflibercept in metastatic colorectal cancer  
*Devaux M, Gerard L, Richard C, Bengrine-Lefevre L, Vincent J, Schmitt A, Ghiringhelli F*

**Retrospective Study**

- 86 Impact of conditioning regimen on peripheral blood hematopoietic cell transplant  
*Burns M, Singh AK, Hoefer CC, Zhang Y, Wallace PK, Chen GL, Platek A, Winslow TB, Iovoli AJ, Choi C, Ross M, McCarthy PL, Hahn T*

**Observational Study**

- 98 Hong Kong female's breast cancer awareness measure: Cross-sectional survey  
*Yeung MPS, Chan EYY, Wong SYS, Yip BHK, Cheung PSY*

## ABOUT COVER

Editorial Board of *World Journal of Clinical Oncology*, Deliang Cao, MD, PhD, Associate Professor, Department of Medical Microbiology, Immunology, and Cell Biology, Simmons Cooper Cancer Institute, Springfield, IL 62794, United States

## AIMS AND SCOPE

*World Journal of Clinical Oncology* (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJCO* covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, *etc.* Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, *etc.*

We encourage authors to submit their manuscripts to *WJCO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

## INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

## RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Yun-Xiaojuan Wu Proofing Editorial Office Director: Jin-Lei Wang

### NAME OF JOURNAL

*World Journal of Clinical Oncology*

### ISSN

ISSN 2218-4333 (online)

### LAUNCH DATE

November 10, 2010

### FREQUENCY

Monthly

### EDITORS-IN-CHIEF

Hiten RH Patel

### EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2218-4333/editorialboard.htm>

### EDITORIAL OFFICE

Jin-Lei Wang, Director

### PUBLICATION DATE

February 24, 2019

### COPYRIGHT

© 2019 Baishideng Publishing Group Inc

### INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

### GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

### GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

### PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

### ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

### STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

### ONLINE SUBMISSION

<https://www.f6publishing.com>



## Pancreatic cancer screening in patients with presumed branch-duct intraductal papillary mucinous neoplasms

Yuichi Torisu, Kazuki Takakura, Yuji Kinoshita, Yoichi Tomita, Masanori Nakano, Masayuki Saruta

**ORCID number:** Yuichi Torisu (0000-0002-2349-8855); Kazuki Takakura (0000-0003-1444-3761); Yuji Kinoshita (0000-0003-1402-5033); Yoichi Tomita (0000-0001-8674-9837); Masanori Nakano (0000-0001-7222-6437); Masayuki Saruta (0000-0001-8172-3240).

**Author contributions:** Torisu Y and Takakura K wrote the manuscript; Kinoshita Y, Tomita Y and Nakano M critically appraised the manuscript; Saruta M formatted and edited the final manuscript.

**Conflict-of-interest statement:** The authors each declare no financial relationships to disclose.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Received:** October 13, 2018

**Peer-review started:** October 15, 2018

**First decision:** November 28, 2018

**Revised:** December 8, 2018

**Accepted:** January 9, 2019

**Yuichi Torisu, Kazuki Takakura, Yuji Kinoshita, Yoichi Tomita, Masanori Nakano, Masayuki Saruta,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, Minato-ku, Tokyo 105-8461, Japan

**Corresponding author:** Yuichi Torisu, MD, PhD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato-ku, Tokyo 105-8461, Japan. [torisu@yb4.so-net.ne.jp](mailto:torisu@yb4.so-net.ne.jp)

**Telephone:** +81-3-34331111

**Fax:** +81-3-34350569

### Abstract

Because delayed diagnosis is one of the causes of poor prognosis in pancreatic ductal adenocarcinoma (PDAC), early detection is a key for overall improvement of prognosis. Towards this end, periodic screening is recommended for individuals considered high-risk for PDAC. Advances in diagnostic imaging modalities have increased the frequency of incidental findings of pancreatic cysts, including the intraductal papillary mucinous neoplasm (IPMN) - a major risk factor of PDAC, having 1% annual prevalence of concomitance with IPMN. Proper retainment of patients with IPMN and regular follow-up by routine imaging examination will likely improve early detection and better prognosis of PDAC. Unfortunately, current guidelines only address management of PDAC derived from IPMN and overlook PDAC concomitant with IPMN. Screening of patients with IPMN, by endoscopic ultrasonography (currently the most reliable modality for detecting small PDAC), may facilitate early detection of both IPMN-derived and -concomitant PDAC. Prospective studies to evaluate the usefulness of endoscopic ultrasonography in screening of IPMN-concomitant PDAC will also help in determining the optimal surveillance strategy for more widespread applications.

**Key words:** Intraductal papillary mucinous neoplasm; Pancreatic ductal adenocarcinoma; Endoscopic ultrasonography; Screening; Early diagnosis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Advances in diagnostic imaging modalities have increased the frequency of incidental findings of pancreatic cysts, including of the intraductal papillary mucinous neoplasm (IPMN) - a major risk factor of pancreatic ductal adenocarcinoma (PDAC). Proper retainment of patients with IPMN and regular follow-up by routine imaging examination will likely improve early detection and better prognosis of PDAC.

**Article in press:** January 10, 2019  
**Published online:** February 24, 2019

Unfortunately, current guidelines only address management of PDAC derived from IPMN and overlook PDAC concomitant with IPMN. Screening of patients with IPMN, by endoscopic ultrasonography (currently the most reliable modality for detecting small PDAC), may facilitate early detection of both IPMN-derived and -concomitant PDAC.

**Citation:** Torisu Y, Takakura K, Kinoshita Y, Tomita Y, Nakano M, Saruta M. Pancreatic cancer screening in patients with presumed branch-duct intraductal papillary mucinous neoplasms. *World J Clin Oncol* 2019; 10(2): 67-74

**URL:** <https://www.wjgnet.com/2218-4333/full/v10/i2/67.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v10.i2.67>

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) persists worldwide as a remarkably lethal malignancy with extremely poor prognosis. The National Cancer Center Japan estimated that 39800 Japanese individuals developed PDAC in 2017, with 34100 among them having died; likewise, the 5-year survival rate for Japanese PDAC patients was only 7.8%. One of major causes of poor prognosis for PDAC is the generally delayed diagnosis, which results in over 90% of diagnoses being made at stages III or IV<sup>[1]</sup>. Egawa *et al*<sup>[2]</sup> reported the 5-year survival rates of PDAC according to the UICC International Union Against Cancer stages (6<sup>th</sup> edition) as 68.7% for stage IA, 59.7% for IB, 30.2% for IIA, 13.3% for IIB, 4.7% for III, and 2.7% for IV. This pattern of steady decline in survival suggests that even if patients with PDAC were to be diagnosed in the earliest stage (I), the prognostic outcomes would still be remarkably poor.

On the contrary, it was reported that the 5-year survival rate for early PDAC of size 10 mm or less was relatively good, at 80.4%; although the detection of such a small size PDAC could be made in up to only 0.8% of the total patient population. The range of challenges to small PDAC detection encompass patient-related features (*e.g.*, asymptomatic presentation) and clinic-related limitations (*e.g.*, lack of established screening guidelines and the limits of visualization in ultrasonography (US), commonly used to observe the whole pancreas in screening). Therefore, periodic screening is recommended for patients with PDAC, especially those identified as high-risk - such as patients with PDAC family history, diabetes mellitus, or chronic pancreatitis<sup>[3-6]</sup>.

Pancreatic cysts, including the intraductal papillary mucinous neoplasms (IPMNs), are another risk factor for PDAC<sup>[7-9]</sup>. Hence, proper identification of affected patients and steady follow-up with routine imaging examinations will likely improve early detection rates and, consequently, prognosis of PDAC. Unfortunately, there remains a lack of coalesced knowledge on IPMN case management for PDAC. This review aimed to provide an informational foundation for a proper screening strategy for follow-up of IPMN cases, for IPMN-concomitant PDAC.

## PREVALENCE OF PANCREATIC CYSTS

With the recent advancements in diagnostic imaging technologies involving magnetic resonance imaging (MRI), the frequency of incidental detection of pancreatic cystic lesions has increased<sup>[10]</sup>. Moreover, the minimum size for detection of a pancreatic cyst has decreased, with solitary cysts of only a few millimeters in size being identifiable<sup>[10]</sup>.

The previous studies on the prevalence of incidental pancreatic cyst are summarized in Table 1. Pancreatic cysts belong to a heterogeneous group of tumors, ranging from benign to malignant<sup>[11]</sup>. The latter includes the precursor lesions of PDAC, such as the IPMNs and mucinous cystic neoplasms<sup>[12]</sup>. The IPMNs are further subdivided according to location in the ducts. The 2017 revised international guidelines<sup>[13]</sup> distinguished IPMNs in the main duct from those in the branch ducts. Specifically, the branch-duct (BD)-IPMN was defined as located in the branch duct with dilation, having > 5 mm cyst size, and interacting with the main pancreatic duct.

An investigation by Kimura *et al*<sup>[14]</sup> of the epithelial growth of small cystic lesions in 300 consecutive autopsy cases found cystic lesions in 24.3% (*n* = 73). Histological analysis identified 47.5% as normal epithelium, 32.8% as papillary hyperplasia

**Table 1 Previous studies on prevalence of incidental pancreatic cysts**

Article	Country	Design	Method of detection	Population	Prevalence, %
Kimura <i>et al</i> <sup>[14]</sup> , 1995	Japan	Retrospective	Autopsy	300 consecutive autopsies in an elderly population	24.3
Zhang <i>et al</i> <sup>[20]</sup> , 2002	United States	Retrospective	1.5 T MRI	1444 patients who underwent a MRI, including 323 patients performed for pancreatic or biliary indication	19.6
Laffan <i>et al</i> <sup>[17]</sup> , 2008	United States	Retrospective	16-MDCT	2832 16-MDCT performed for nonpancreatic indication	2.6
Lee <i>et al</i> <sup>[21]</sup> , 2010	United States	Retrospective	1.5 T MRI	616 MRI performed for nonpancreatic indication	13.5
Girometti <i>et al</i> <sup>[16]</sup> , 2011	Italy	Retrospective	1.5 T MRI	152 MRI performed for nonpancreatic indication	44.7
Ip <i>et al</i> <sup>[18]</sup> , 2011	United States	Retrospective	CT or MRI*	17443 patients who underwent a CT and 2700 patients who underwent a MRI	CT 2.2, MRI 15.9
Matsubara <i>et al</i> <sup>[22]</sup> , 2012	Japan	Retrospective	1.5 T MRI	1226 MRI performed for nonpancreatic indication	10
Sey <i>et al</i> <sup>[23]</sup> , 2015	United States	Prospective	EUS	341 EUS performed for nonpancreatic indication	9.4
Soroida <i>et al</i> <sup>[19]</sup> , 2016	Japan	Retrospective	US	5198 US performed as part of a general health examination	3.5
Moris <i>et al</i> <sup>[10]</sup> , 2016	United States	Retrospective	1.5 T or 3 T MRI	500 MRI performed for nonpancreatic indication	41.6
Martínez <i>et al</i> <sup>[24]</sup> , 2018	Spain	Prospective	EUS	298 EUS performed for nonpancreatic indication	21.5

\*There is no description of the MRI instrument model. CT: Computed tomography; EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; PDAC: Pancreatic ductal adenocarcinoma; US: Ultrasonography.

without atypia, 16.4% as atypical hyperplasia, and 3.4% as carcinoma *in situ*. Apparently, the cystic lesions without normal epithelium were equivalent to IPMN. In addition, Fernández-del Castillo *et al*<sup>[15]</sup> reported that most pancreatic cysts are mucinous cystic tumors (including IPMNs), and Girometti *et al*<sup>[16]</sup> found that 70.6% of the detected pancreatic cysts presented IPMN-like patterns (*i.e.*, polycystic, main pancreatic duct interaction, and > 5 mm) or an indeterminate pattern. Considering these collective data, it seems that the majority of pancreatic cysts are actually representatives of IPMNs.

The reported prevalence rates for pancreatic cysts have varied depending on the imaging method used for detection. Namely, the reported detection rates have been for 2.2%-2.6%<sup>[17,18]</sup> for computed tomography (CT), 3.5%<sup>[19]</sup> for US, 10%-44.7%<sup>[10,16,18,20-22]</sup> for MRI, and 9.4%-21.5%<sup>[23,24]</sup> for endoscopic ultrasonography (EUS). A similar amount of reports<sup>[10,14,16,17,19-21,23,24]</sup> have demonstrated aging as a significant risk factor for pancreatic cysts; in general, the frequency of pancreatic cysts among the elderly is over 20%.

## PDAC CONCOMITANT WITH IPMN

### Definitions of PDAC concomitant with IPMN and PDAC derived from IPMN

Unlike the PDAC derived from IPMN, PDAC occurring concomitantly with IPMN features PDAC and IPMN that developed from different parts of the pancreatic



parenchyma. It has been suggested that these two forms of PDAC - that derived from IPMN and that concomitant with IPMN - should be considered as different diseases<sup>[25]</sup>. However, in the case of PDAC having developed from tissue adjacent to the IPMN, the distinction between PDAC derived from IPMN and PDAC concomitant with IPMN will be difficult. Molecular biomarkers, including the expression profile of MUC and the mutational status of GNAS and KRAS, may help to distinguish these two types of PDAC more clearly<sup>[26,27]</sup>.

### **Assessment of concomitant PDAC in surgically resected IPMN**

There have been several studies for PDAC concomitant with IPMN since the first report in 2002 by Yamaguchi *et al*<sup>[28]</sup>. The reported incidence rates of PDAC concomitant with IPMN are 9%<sup>[28]</sup> and 4%<sup>[29]</sup>, determined in two studies of surgically resected IPMN case series. Ingkakul *et al*<sup>[30]</sup> found that 9.3% ( $n = 22$ ) of patients with IPMN ( $n = 236$ ) had concomitant PDAC, either synchronously or metachronously. In addition, Yamaguchi *et al*<sup>[25]</sup> found 31 cases of PDAC concomitant with IPMN among 765 IPMN resections. However, it seems that these results might represent underestimations of the actual number of cases of PDAC concomitant with IPMN because of the study design used (*i.e.*, retrospective evaluation of surgically resected specimens).

Conversely, Matsubara *et al*<sup>[22]</sup> reported that, among a total of 116 PDAC patients, 65 (56%) presented with both PDAC and pancreatic cysts. Moreover, 5 presented with cystic lesions (identified at least 2 year before the PDAC diagnosis) located upstream of the PDAC and 28 with lesions downstream of the PDAC. These 33 cases with pancreatic cystic lesions were classified as “preexisting” PDAC, and accounted for 28% of the total 116 patients evaluated. Accordingly, the actual frequency of PDAC concomitant with IPMN might be higher than the rates reported to date.

### **Frequency of PDAC concomitant with IPMN among patients with BD-IPMNs**

The previous studies that have examined the duration of concomitant PDAC development during the follow-up period for IPMNs are summarized in [Table 2](#)<sup>[7-9,31-37]</sup>. Interestingly, the incidence of PDAC concomitant with IPMN tends to be higher in Japan (about 1% per year<sup>[7,8]</sup>), as compared to the reports from the United States and Italy. One of the Japanese studies, by Tanno *et al*<sup>[8]</sup>, investigated 89 BD-IPMN patients without any mural nodule and followed each up for at least 2 year (median: 64 mo; range: 25-158 mo), and identified 4 cases of PDACs located distant from the BD-IPMN in 552 patient-years of follow-up (7.2 per 1000 patient-years).

Another Japanese study, by Maguchi *et al*<sup>[9]</sup>, analyzed 349 follow-up BD-IPMN patients who had no mural nodules on EUS exam at initial diagnosis, and identified 7 (2.0%) concomitant PDAC cases within the follow-up period (median: 3.7 year; range: 1-16.3 year). Likewise, Kamata *et al*<sup>[36]</sup> showed a 6.9% incidence of concomitant PDAC development in 102 BD-IPMN patients without mural nodule during the follow-up period (median: 42 mo). Finally, Uehara *et al*<sup>[7]</sup> found a 1.1% per year incidence of PDAC among patients with BD-IPMN, whereas the expected incidence of PDAC in the age- and gender-matched control group was calculated to be 0.045% per year.

Taken together, the frequency of concomitant PDAC in Japanese patients with BD-IPMNs is not low, suggesting that these patients should be considered for a screening strategy, particularly examining the whole pancreas.

### **Characteristics of PDAC concomitant with IPMN**

As described above, screenings for patients with IPMN should be conducted not only to monitor the primary IPMN lesions but also to track the possible development of concomitant PDAC. However, due to the large number of IPMN patients, it will be important to limit the surveillance target population and to decide on the appropriate screening interval for the imaging examinations. Understanding the distinctive characteristics of PDAC concomitant with IPMN may be helpful for determining the optimal detection parameters of PDAC.

Tanno *et al*<sup>[8]</sup> reported that the incidence of PDACs located distant from the BD-IPMNs was significantly higher for older patients ( $> 70$  year) and for women. Ideno *et al*<sup>[26,28]</sup> showed that distinct PDACs frequently develop in the pancreas presenting benign gastric-type IPMN without GNAS mutations. In addition, it had been reported that IPMN patients with a family history of PDAC are at higher risk of developing PDAC concomitant with IPMN. A study by Nehra *et al*<sup>[39]</sup> of 324 patients with resected IPMNs revealed that patients with a family history of PDAC developed concomitant PDAC more frequently than did those without (11.1% *vs* 2.9%,  $P = 0.002$ ). Likewise, a study of 300 patients with IPMN by Mandai *et al*<sup>[40]</sup> revealed that concomitant PDAC occurred more frequently in patients with affected first-degree relatives than in those without (17.6% *vs* 2.1%,  $P = 0.01$ ). Thus, individuals with the above characteristics

**Table 2** Frequency of concomitant pancreatic ductal adenocarcinoma in patients with branch-duct - intraductal papillary mucinous neoplasm during follow-up

Article	Country	Design	n	Diameter of IPMN in mm*	Follow-up in mo*	Surveillance interval	Imaging(optional imaging)	Incidence of concomitant PDAC, n (%)
Kobayashi <i>et al</i> <sup>[31]</sup> , 2005	Japan	Retrospective	47	28.2	41.0	No description	EUS	3 (6.4)
Tada <i>et al</i> <sup>[32]</sup> , 2006	Japan	Prospective	80	22.0	48.0	q6 mo	US, CT, MRI, EUS	2 (2.5)
Uehara <i>et al</i> <sup>[7]</sup> , 2008	Japan	Retrospective	60	No description	87.0	q3-6 mo	US (CT, MRI, EUS)	5 (8.3)
Sawai <i>et al</i> <sup>[33]</sup> , 2010	Japan	Retrospective	103	18.0	59.0	At least yearly	EUS	2 (1.9)
Tanno <i>et al</i> <sup>[8]</sup> , 2010	Japan	Prospective	89	20.0	64.0	q6-12 mo	CT, MRI, EUS	4 (4.5)
Maguchi <i>et al</i> <sup>[9]</sup> , 2011	Japan	Retrospective	349	19.0	44.0	No description	US, CT, MRI, EUS, ERCP	7 (2.0)
Ohno <i>et al</i> <sup>[34]</sup> , 2012	Japan	Retrospective	142	22.3	42.5	q6 mo	CE-EUS, CT	5 (3.5)
Sahora <i>et al</i> <sup>[35]</sup> , 2013	United States	Retrospective	411	16.0	60.0	q3-24 mo	CT, MRI	3 (0.7)
Kamata <i>et al</i> <sup>[36]</sup> , 2014	Japan	Retrospective	102	No description	42.0	q3 mo	US, CT, MRI, EUS	7 (6.9)
Malleo <i>et al</i> <sup>[37]</sup> , 2015	Italy	Prospective	569	18.0	56.0	At least yearly	MRI (EUS)	3 (0.5)

\*Mean, or, if not available, median or midpoint of range. CT: Computed tomography; EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; PDAC: Pancreatic ductal adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm; US: Ultrasonography.

have a higher risk of PDAC and should be checked more attentively for early detection of concomitant PDAC.

Collective studies have shown that malignancy of primary IPMNs does not correlate with incidence of concomitant PDAC. Tada *et al*<sup>[32]</sup> reported that IPMNs with concomitant PDAC found in cases with small cyst diameter are probably indicative of benign IPMNs. Also, Ingkakul *et al*<sup>[30]</sup> reported that, in their study population, all of the detected concomitant PDAC cases involved patients with BD-IPMN or BD-IPM adenoma. The current IPMN guidelines<sup>[13,41]</sup> describe surveillance strategies for PDAC derived from IPMN and state that the smaller the size of the IPMN, the longer the interval between screening examinations. In addition, the American Gastroenterological Association guidelines<sup>[41]</sup> recommend canceling the follow-up if there are no changes within 5 year; although, Mandai *et al*<sup>[40]</sup> reported that 6 of 9 concomitant PDAC cases were detected at 6 year or later after the detection of IPMN. Thus, a more cautious screening strategy may be essential for early detection of concomitant PDAC in the patients with BD-IPMN.

#### **Imaging modalities for early detection of PDAC concomitant with BD-IPMN**

In recent years, several imaging modalities have been applied in surveillance of BD-IPMN; these include US, CT, MRI and EUS. However, it is still unclear which of these imaging modalities should be selected for screening and what the optimal length of interval is for each in follow-up, to best achieve early detection of both IPMN-derived and -concomitant PDAC. As described above, while current guidelines<sup>[13,41]</sup> mention surveillance strategies for PDAC derived from IPMN, these remarks are, unfortunately, irrelevant for the early detection of IPMN-concomitant PDAC.

Kanno *et al*<sup>[42]</sup> retrospectively analyzed 200 PDAC cases of stage 0 and stage I, and identified the dilated main pancreatic duct as an indirect imaging feature of early PDAC - detectable to a similar degree in all imaging modalities: 74.8% in US, 79.6% in CT, 82.7% in MRI, and 88.4% in EUS. In contrast, direct imaging features of early PDAC could be seen most clearly in EUS (76.3%) compared with the others (52.6% in US, 51.5% in CT, and 45.1% in MRI). Kamata *et al*<sup>[36]</sup> reported that among the 102 BD-IPMN patients without mural nodule, who were followed-up with image diagnosis every 3 mo (by EUS semiannually and by US/CT and MRI annually, performed respectively between the two EUS examinations), 7(6.9%) developed concomitant PDAC, with an average diameter of 16 mm (range: 7-30 mm) during the follow-up period (median: 42 mo; range, 12-74 mo). The study also determined that EUS was the



only imaging modality capable of detecting concomitant PDAC at a curable stage; the detection rates of PDAC concomitant with IPMN during the follow-up period were 100% by EUS, 0% by US, 43% by CT and 43% by MRI.

Although EUS was demonstrated to be superior in detecting PDAC concomitant with IPMN, another previous study demonstrated that EUS does not have marginal use in surveillance of BD-IPMNs<sup>[43]</sup>. In particular, the statistical associations of EUS with different rates of morphologic progression, surgery, malignancy and death all fell below the threshold of significance. However, the meta-analysis had some limitations in the study design that may have impacted the results - namely, that most included articles reported on retrospective studies and that several of the studies included data from patients who were followed up with EUS at long intervals.

Hopefully, future prospective studies will be conducted to confirm the usefulness of EUS in surveillance of patients with IPMNs for potential development of concomitant PDAC. Furthermore, these studies are necessary to determine the optimal surveillance strategy (intervals and imaging modalities) for BD-IPMN patients in particular. As this is an ongoing unresolved health issue, impacting populations across the globe, there is urgency to performing such studies.

## CONCLUSION

Appropriate retainment of patients with IPMNs, especially those with BD-IPMNs, for periodic screening with routine imaging examinations, particularly EUS, will help to promote early detection and better prognosis of both IPMN-derived and -concomitant PDAC. To this end, further evaluations are needed to confirm the most efficient surveillance strategies for presumed BD-IPMN.

## REFERENCES

- 1 **Bierley JD**, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. Wiley: Blackwell 2017;
- 2 **Egawa S**, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Yanagisawa A, Tanaka M. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. *Pancreas* 2012; **41**: 985-992 [PMID: 22750974 DOI: 10.1097/MPA.0b013e318258055c]
- 3 **Permeth-Wey J**, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. *Fam Cancer* 2009; **8**: 109-117 [PMID: 18763055 DOI: 10.1007/s10689-008-9214-8]
- 4 **Matsubayashi H**, Maeda A, Kanemoto H, Uesaka K, Yamazaki K, Hironaka S, Miyagi Y, Ikehara H, Ono H, Klein A, Goggins M. Risk factors of familial pancreatic cancer in Japan: current smoking and recent onset of diabetes. *Pancreas* 2011; **40**: 974-978 [PMID: 21487321 DOI: 10.1097/MPA.0b013e3182156e1b]
- 5 **Brune KA**, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, Klein AP. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010; **102**: 119-126 [PMID: 20068195 DOI: 10.1093/jnci/djp466]
- 6 **Hong SM**, Park JY, Hruban RH, Goggins M. Molecular signatures of pancreatic cancer. *Arch Pathol Lab Med* 2011; **135**: 716-727 [PMID: 21631264 DOI: 10.1043/2010-0566-RA.1]
- 7 **Uehara H**, Nakaizumi A, Ishikawa O, Iishi H, Tatsumi K, Takakura R, Ishida T, Takano Y, Tanaka S, Takenaka A. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. *Gut* 2008; **57**: 1561-1565 [PMID: 18477671 DOI: 10.1136/gut.2007.145631]
- 8 **Tanno S**, Nakano Y, Koizumi K, Sugiyama Y, Nakamura K, Sasajima J, Nishikawa T, Mizukami Y, Yanagawa N, Fujii T, Okumura T, Obara T, Kohgo Y. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. *Pancreas* 2010; **39**: 36-40 [PMID: 19745777 DOI: 10.1097/MPA.0b013e3181b91cd0]
- 9 **Maguchi H**, Tanno S, Mizuno N, Hanada K, Kobayashi G, Hatori T, Sadakari Y, Yamaguchi T, Tobita K, Doi R, Yanagisawa A, Tanaka M. Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. *Pancreas* 2011; **40**: 364-370 [PMID: 21289527 DOI: 10.1097/MPA.0b013e31820a5975]
- 10 **Moris M**, Bridges MD, Pooley RA, Raimondo M, Woodward TA, Stauffer JA, Asbun HJ, Wallace MB. Association Between Advances in High-Resolution Cross-Section Imaging Technologies and Increase in Prevalence of Pancreatic Cysts From 2005 to 2014. *Clin Gastroenterol Hepatol* 2016; **14**: 585-593.e3 [PMID: 26370569 DOI: 10.1016/j.cgh.2015.08.038]
- 11 **Basturk O**, Coban I, Adsay NV. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med* 2009; **133**: 423-438 [PMID: 19260748 DOI: 10.1043/1543-2165-133.3.423]
- 12 **Distler M**, Aust D, Weitz J, Pilarsky C, Grützmann R. Precursor lesions for sporadic pancreatic cancer: PanIN, IPMN, and MCN. *Biomed Res Int* 2014; **2014**: 474905 [PMID: 24783207 DOI: 10.1155/2014/474905]
- 13 **Tanaka M**, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatol* 2017; **17**: 738-753 [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007]
- 14 **Kimura W**, Nagai H, Kuroda A, Muto T, Esaki Y. Analysis of small cystic lesions of the pancreas. *Int J*

- Pancreatol* 1995; **18**: 197-206 [PMID: 8708390 DOI: 10.1007/BF02784942]
- 15 **Fernández-del Castillo C**, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg* 2003; **138**: 427-3; discussion 433-4 [PMID: 12686529 DOI: 10.1001/archsurg.138.4.427]
  - 16 **Girometti R**, Intini S, Brondani G, Como G, Londero F, Bresadola F, Zuiani C, Bazzocchi M. Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: prevalence and relation with clinical and imaging features. *Abdom Imaging* 2011; **36**: 196-205 [PMID: 20473669 DOI: 10.1007/s00261-010-9618-4]
  - 17 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]
  - 18 **Ip IK**, Mortelet KJ, Prevedello LM, Khorasani R. Focal cystic pancreatic lesions: assessing variation in radiologists' management recommendations. *Radiology* 2011; **259**: 136-141 [PMID: 21292867 DOI: 10.1148/radiol.10100970]
  - 19 **Soroida Y**, Sato M, Hikita H, Hagiwara S, Sato M, Gotoh H, Kato S, Iwai T, Yamazaki T, Yatomi Y, Sasano T, Ikeda H. Pancreatic cysts in general population on ultrasonography: Prevalence and development of risk score. *J Gastroenterol* 2016; **51**: 1133-1140 [PMID: 26988361 DOI: 10.1007/s00535-016-1196-y]
  - 20 **Zhang XM**, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology* 2002; **223**: 547-553 [PMID: 11997566 DOI: 10.1148/radiol.2232010815]
  - 21 **Lee KS**, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010; **105**: 2079-2084 [PMID: 20354507 DOI: 10.1038/ajg.2010.122]
  - 22 **Matsubara S**, Tada M, Akahane M, Yagioka H, Kogure H, Sasaki T, Arizumi T, Togawa O, Nakai Y, Sasahira N, Hirano K, Tsujino T, Isayama H, Toda N, Kawabe T, Ohtomo K, Omata M. Incidental pancreatic cysts found by magnetic resonance imaging and their relationship with pancreatic cancer. *Pancreas* 2012; **41**: 1241-1246 [PMID: 22699201 DOI: 10.1097/MPA.0b013e31824f5970]
  - 23 **Sey MS**, Teagarden S, Settles D, McGreevy K, Coté GA, Sherman S, McHenry L, LeBlanc JK, Al-Haddad M, DeWitt JM. Prospective Cross-Sectional Study of the Prevalence of Incidental Pancreatic Cysts During Routine Outpatient Endoscopic Ultrasound. *Pancreas* 2015; **44**: 1130-1133 [PMID: 26335009 DOI: 10.1097/MPA.0000000000000408]
  - 24 **Martínez B**, Martínez JF, Aparicio JR. Prevalence of incidental pancreatic cyst on upper endoscopic ultrasound. *Ann Gastroenterol* 2018; **31**: 90-95 [PMID: 29333072 DOI: 10.20524/aog.2017.0211]
  - 25 **Yamaguchi K**, Kanemitsu S, Hatori T, Maguchi H, Shimizu Y, Tada M, Nakagohri T, Hanada K, Osanai M, Noda Y, Nakaizumi A, Furukawa T, Ban S, Nobukawa B, Kato Y, Tanaka M. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. *Pancreas* 2011; **40**: 571-580 [PMID: 21499212 DOI: 10.1097/MPA.0b013e318215010c]
  - 26 **Ideno N**, Ohtsuka T, Matsunaga T, Kimura H, Watanabe Y, Tamura K, Aso T, Aishima S, Miyasaka Y, Ohuchida K, Ueda J, Takahata S, Oda Y, Mizumoto K, Tanaka M. Clinical significance of GNAS mutation in intraductal papillary mucinous neoplasm of the pancreas with concomitant pancreatic ductal adenocarcinoma. *Pancreas* 2015; **44**: 311-320 [PMID: 25479586 DOI: 10.1097/MPA.0000000000000258]
  - 27 **Tamura K**, Ohtsuka T, Date K, Fujimoto T, Matsunaga T, Kimura H, Watanabe Y, Miyazaki T, Ohuchida K, Takahata S, Ishigami K, Oda Y, Mizumoto K, Nakamura M, Tanaka M. Distinction of Invasive Carcinoma Derived From Intraductal Papillary Mucinous Neoplasms From Concomitant Ductal Adenocarcinoma of the Pancreas Using Molecular Biomarkers. *Pancreas* 2016; **45**: 826-835 [PMID: 26646266 DOI: 10.1097/MPA.0000000000000563]
  - 28 **Yamaguchi K**, Ohuchida J, Ohtsuka T, Nakano K, Tanaka M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. *Pancreatol* 2002; **2**: 484-490 [PMID: 12378117 DOI: 10.1159/000064716]
  - 29 **Kamisawa T**, Tu Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Malignancies associated with intraductal papillary mucinous neoplasm of the pancreas. *World J Gastroenterol* 2005; **11**: 5688-5690 [PMID: 16237766 DOI: 10.3748/wjg.v11.i36.5688]
  - 30 **Ingkakul T**, Sadakari Y, Ienaga J, Satoh N, Takahata S, Tanaka M. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg* 2010; **251**: 70-75 [PMID: 20009749 DOI: 10.1097/SLA.0b013e3181c5ddc3]
  - 31 **Kobayashi G**, Fujita N, Noda Y, Ito K, Horaguchi J, Takasawa O, Akaishi S, Tsuchiya T, Kobari M. Mode of progression of intraductal papillary-mucinous tumor of the pancreas: analysis of patients with follow-up by EUS. *J Gastroenterol* 2005; **40**: 744-751 [PMID: 16082592 DOI: 10.1007/s00535-005-1619-7]
  - 32 **Tada M**, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Tateishi K, Isayama H, Toda N, Yoshida H, Omata M. Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. *Clin Gastroenterol Hepatol* 2006; **4**: 1265-1270 [PMID: 16979953 DOI: 10.1016/j.cgh.2006.07.013]
  - 33 **Sawai Y**, Yamao K, Bhatia V, Chiba T, Mizuno N, Sawaki A, Takahashi K, Tajika M, Shimizu Y, Yatabe Y, Yanagisawa A. Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms. *Endoscopy* 2010; **42**: 1077-1084 [PMID: 21120776 DOI: 10.1055/s-0030-1255971]
  - 34 **Ohno E**, Itoh A, Kawashima H, Ishikawa T, Matsubara H, Itoh Y, Nakamura Y, Hiramatsu T, Nakamura M, Miyahara R, Ohmiya N, Ishigami M, Katano Y, Goto H, Hirooka Y. Malignant transformation of branch duct-type intraductal papillary mucinous neoplasms of the pancreas based on contrast-enhanced endoscopic ultrasonography morphological changes: focus on malignant transformation of intraductal papillary mucinous neoplasm itself. *Pancreas* 2012; **41**: 855-862 [PMID: 22481289 DOI: 10.1097/MPA.0b013e3182480c44]
  - 35 **Sahora K**, Mino-Kenudson M, Brugge W, Thayer SP, Ferrone CR, Sahani D, Pitman MB, Warshaw AL, Lillemoe KD, Fernandez-del Castillo CF. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg* 2013; **258**: 466-475 [PMID: 24022439 DOI: 10.1097/SLA.0b013e3182a18f48]
  - 36 **Kamata K**, Kitano M, Kudo M, Sakamoto H, Kadosaka K, Miyata T, Imai H, Maekawa K, Chikugo T, Kumano M, Hyodo T, Murakami T, Chiba Y, Takeyama Y. Value of EUS in early detection of pancreatic

- ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms. *Endoscopy* 2014; **46**: 22-29 [PMID: [24218310](#) DOI: [10.1055/s-0033-1353603](#)]
- 37 **Malleo G**, Marchegiani G, Borin A, Capelli P, Accordini F, Butturini G, Pederzoli P, Bassi C, Salvia R. Observational study of the incidence of pancreatic and extrapancreatic malignancies during surveillance of patients with branch-duct intraductal papillary mucinous neoplasm. *Ann Surg* 2015; **261**: 984-990 [PMID: [25493361](#) DOI: [10.1097/SLA.0000000000000884](#)]
- 38 **Ideno N**, Ohtsuka T, Kono H, Fujiwara K, Oda Y, Aishima S, Ito T, Ishigami K, Tokunaga S, Ohuchida K, Takahata S, Nakamura M, Mizumoto K, Tanaka M. Intraductal papillary mucinous neoplasms of the pancreas with distinct pancreatic ductal adenocarcinomas are frequently of gastric subtype. *Ann Surg* 2013; **258**: 141-151 [PMID: [23532108](#) DOI: [10.1097/SLA.0b013e31828cd008](#)]
- 39 **Nehra D**, Oyarvide VM, Mino-Kenudson M, Thayer SP, Ferrone CR, Wargo JA, Muzikansky A, Finkelstein D, Warshaw AL, Castillo CF. Intraductal papillary mucinous neoplasms: does a family history of pancreatic cancer matter? *Pancreatology* 2012; **12**: 358-363 [PMID: [22898638](#) DOI: [10.1016/j.pan.2012.05.011](#)]
- 40 **Mandai K**, Uno K, Yasuda K. Does a family history of pancreatic ductal adenocarcinoma and cyst size influence the follow-up strategy for intraductal papillary mucinous neoplasms of the pancreas? *Pancreas* 2014; **43**: 917-921 [PMID: [24743378](#) DOI: [10.1097/MPA.0000000000000132](#)]
- 41 **Scheiman JM**, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015; **148**: 824-824.e22 [PMID: [25805376](#) DOI: [10.1053/j.gastro.2015.01.014](#)]
- 42 **Kanno A**, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, Hasebe O, Ohtsuka T, Nakamura M, Takenaka M, Kitano M, Kikuyama M, Gabata T, Yoshida K, Sasaki T, Serikawa M, Furukawa T, Yanagisawa A, Shimosegawa T; Japan Study Group on the Early Detection of Pancreatic Cancer (JEDPAC). Multicenter study of early pancreatic cancer in Japan. *Pancreatology* 2018; **18**: 61-67 [PMID: [29170051](#) DOI: [10.1016/j.pan.2017.11.007](#)]
- 43 **Ooka K**, Rustagi T, Evans A, Farrell JJ. Surveillance and Outcomes of Nonresected Presumed Branch-Duct Intraductal Papillary Mucinous Neoplasms: A Meta-analysis. *Pancreas* 2017; **46**: 927-935 [PMID: [28697134](#) DOI: [10.1097/MPA.0000000000000858](#)]

**P- Reviewer:** Cidon EU, Coskun A, Dumitraşcu T, Kupeli S, Tchilikidi KY, Tang Y

**S- Editor:** Dou Y **L- Editor:** A **E- Editor:** Wu YXJ





Published By Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

