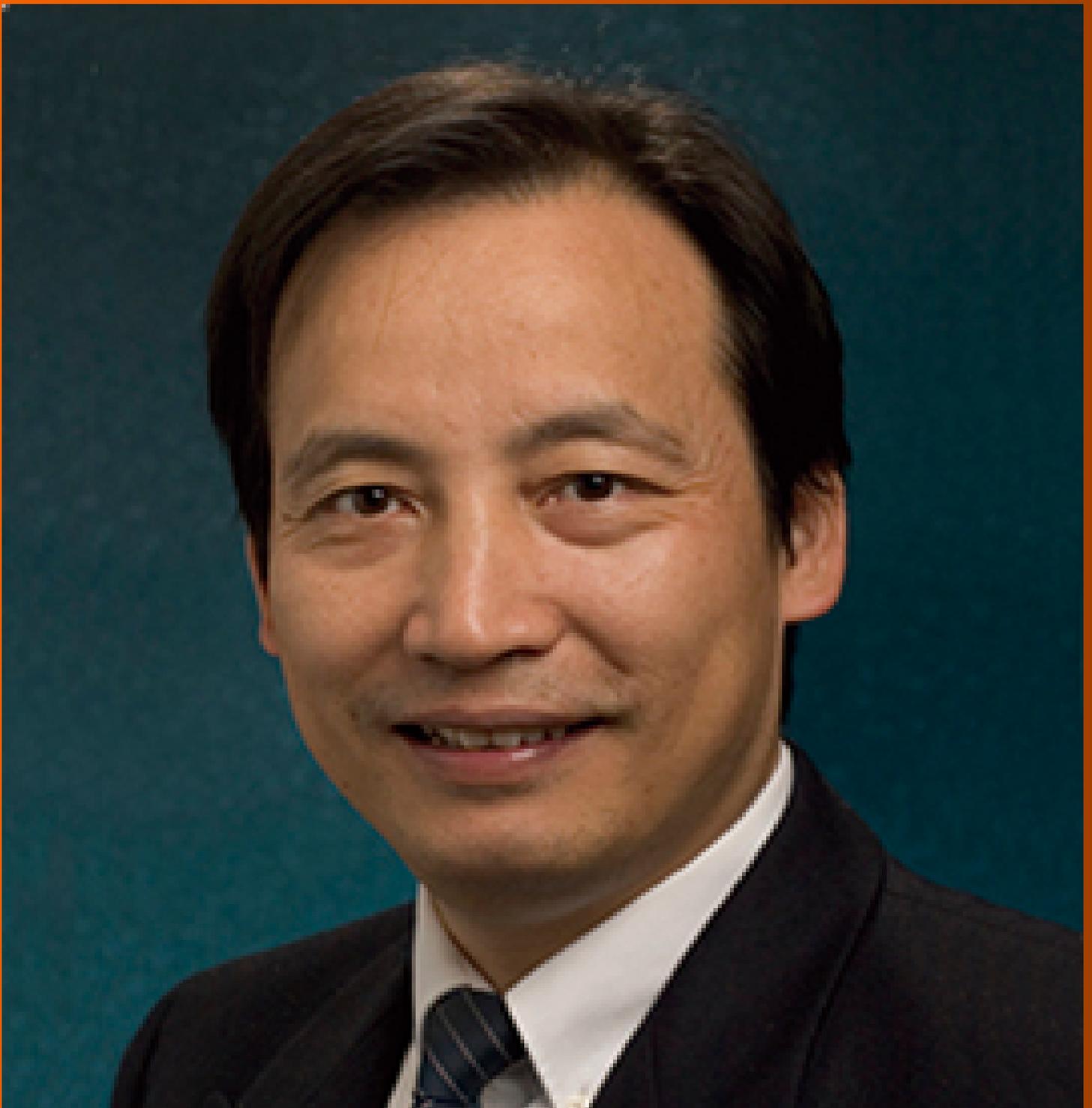


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Pancreatic cancer screening in patients with presumed branch-duct intraductal papillary mucinous neoplasms

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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

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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.

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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^[1]. Egawa *et al*^[2] reported the 5-year survival rates of PDAC according to the UICC International Union Against Cancer stages (6th 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^[3-6].

Pancreatic cysts, including the intraductal papillary mucinous neoplasms (IPMNs), are another risk factor for PDAC^[7-9]. 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^[10]. Moreover, the minimum size for detection of a pancreatic cyst has decreased, with solitary cysts of only a few millimeters in size being identifiable^[10].

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^[11]. The latter includes the precursor lesions of PDAC, such as the IPMNs and mucinous cystic neoplasms^[12]. The IPMNs are further subdivided according to location in the ducts. The 2017 revised international guidelines^[13] 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*^[14] 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> ^[14] , 1995	Japan	Retrospective	Autopsy	300 consecutive autopsies in an elderly population	24.3
Zhang <i>et al</i> ^[20] , 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> ^[17] , 2008	United States	Retrospective	16-MDCT	2832 16-MDCT performed for nonpancreatic indication	2.6
Lee <i>et al</i> ^[21] , 2010	United States	Retrospective	1.5 T MRI	616 MRI performed for nonpancreatic indication	13.5
Girometti <i>et al</i> ^[16] , 2011	Italy	Retrospective	1.5 T MRI	152 MRI performed for nonpancreatic indication	44.7
Ip <i>et al</i> ^[18] , 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> ^[22] , 2012	Japan	Retrospective	1.5 T MRI	1226 MRI performed for nonpancreatic indication	10
Sey <i>et al</i> ^[23] , 2015	United States	Prospective	EUS	341 EUS performed for nonpancreatic indication	9.4
Soroida <i>et al</i> ^[19] , 2016	Japan	Retrospective	US	5198 US performed as part of a general health examination	3.5
Moris <i>et al</i> ^[10] , 2016	United States	Retrospective	1.5 T or 3 T MRI	500 MRI performed for nonpancreatic indication	41.6
Martínez <i>et al</i> ^[24] , 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*^[15] reported that most pancreatic cysts are mucinous cystic tumors (including IPMNs), and Girometti *et al*^[16] 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%^[17,18] for computed tomography (CT), 3.5%^[19] for US, 10%-44.7%^[10,16,18,20-22] for MRI, and 9.4%-21.5%^[23,24] for endoscopic ultrasonography (EUS). A similar amount of reports^[10,14,16,17,19-21,23,24] 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^[25]. 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^[26,27].

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*^[28]. The reported incidence rates of PDAC concomitant with IPMN are 9%^[28] and 4%^[29], determined in two studies of surgically resected IPMN case series. Ingkakul *et al*^[30] found that 9.3% ($n = 22$) of patients with IPMN ($n = 236$) had concomitant PDAC, either synchronously or metachronously. In addition, Yamaguchi *et al*^[25] 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*^[22] 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](#)^[7-9,31-37]. Interestingly, the incidence of PDAC concomitant with IPMN tends to be higher in Japan (about 1% per year^[7,8]), as compared to the reports from the United States and Italy. One of the Japanese studies, by Tanno *et al*^[8], 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*^[9], 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*^[36] 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*^[7] 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*^[8] 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*^[26,28] 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*^[39] 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*^[40] 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(optimal imaging)	Incidence of concomitant PDAC, n (%)
Kobayashi <i>et al</i> ^[31] , 2005	Japan	Retrospective	47	28.2	41.0	No description	EUS	3 (6.4)
Tada <i>et al</i> ^[32] , 2006	Japan	Prospective	80	22.0	48.0	q6 mo	US, CT, MRI, EUS	2 (2.5)
Uehara <i>et al</i> ^[37] , 2008	Japan	Retrospective	60	No description	87.0	q3-6 mo	US (CT, MRI, EUS)	5 (8.3)
Sawai <i>et al</i> ^[33] , 2010	Japan	Retrospective	103	18.0	59.0	At least yearly	EUS	2 (1.9)
Tanno <i>et al</i> ^[8] , 2010	Japan	Prospective	89	20.0	64.0	q6-12 mo	CT, MRI, EUS	4 (4.5)
Maguchi <i>et al</i> ^[9] , 2011	Japan	Retrospective	349	19.0	44.0	No description	US, CT, MRI, EUS, ERCP	7 (2.0)
Ohno <i>et al</i> ^[34] , 2012	Japan	Retrospective	142	22.3	42.5	q6 mo	CE-EUS, CT	5 (3.5)
Sahora <i>et al</i> ^[35] , 2013	United States	Retrospective	411	16.0	60.0	q3-24 mo	CT, MRI	3 (0.7)
Kamata <i>et al</i> ^[36] , 2014	Japan	Retrospective	102	No description	42.0	q3 mo	US, CT, MRI, EUS	7 (6.9)
Malleo <i>et al</i> ^[37] , 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*^[32] reported that IPMNs with concomitant PDAC found in cases with small cyst diameter are probably indicative of benign IPMNs. Also, Ingkakul *et al*^[30] 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^[13,41] 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^[41] recommend canceling the follow-up if there are no changes within 5 year; although, Mandai *et al*^[40] 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^[13,41] mention surveillance strategies for PDAC derived from IPMN, these remarks are, unfortunately, irrelevant for the early detection of IPMN-concomitant PDAC.

Kanno *et al*^[42] 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*^[36] 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^[43]. 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.

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