Branch Duct Intraductal Papillary Mucinous Neoplasm (BD-IPMN): Comparing the detection yield of ERCP, MRCP and EUS

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ABSTRACT

Intraductal papillary mucinous neoplasms as tumor structures are formed in mucin-producing columnar cells of pancreas. Three types of Intraductal papillary mucinous neoplasms have been described including main duct, branch duct and mixed typed. Branch duct intraductal papillary mucinous neoplasm involves the branch duct of wirsung duct. In this review unlike the other ones with similar topics our focus is on the branch duct intraductal papillary mucinous neoplasm and especially about comparing the method for its diagnosing. There are various modalities which can be used in setting of diagnosis classification and management of branch duct intraductal papillary mucinous neoplasms,hence in our study we will assess the diagnostic yield of endoscopic ultrasound, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography for branch duct intraductal papillary mucinous neoplasms. Endoscopic ultrasound, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography are three precise modalities that will be discussed. Our review evaluates each of them and their role in diagnosing branch duct intraductal papillary mucinous neoplasms. Initially it is necessary to have an overview of branch duct intraductal papillary mucinous neoplasms carefully then classification of diagnostic tools, specificity and sensitivity of them are discussed separately. Finally each modality including endoscopic ultrasound, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography have been compared together and the diagnostic yield of each modality has been explained in detail. Because of the significant role of magnetic resonance imaging and computed tomography scan, these modalities have been considered in addition to the major topic tools. At the last part the potential role of the other new technologies in managing of branch duct intraductal papillary mucinous neoplasms in the future are discussed.

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) are some tumor structures that are developed in ducts of pancreas composed of mucin-producing columnar cells [1]. IPMNs are responsible for less than 1-2% (about 2.5% in some studies) [2] of all neoplasms of the pancreas and do not have any particular sign and symptoms [3] while some of them can present with jaundice and acute pancreatitis. Three types of IPMNs have been investigated including main duct (MD-IPMN), branch duct (BD-IPMN) and mixed type. In spite of rare incidence of IPMNs (0.48-2.04 per 100000 persons), with widespread use of newly advanced imaging modalities such as computed tomography scan (CT scan) or magnetic resonance imaging (MRI)/ magnetic resonance cholangiopancreatography (MRCP) frequency of disease has been increased over the past years. Although most BD-IPMNs are benign they harbor increased risk of developing distinct pancreatic ductal adenocarcinoma that makes their appropriate management more challenging. Despite recent advances in imaging modalities of pancreas the diagnosis, treatment, and surveillance of branch duct (BD) IPMN remain unclear [4]. The aim of this review is to compare diagnostic yield of different modalities including MRCP, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) in detection of BD-IPMN.

Received February 09th, 2017- Accepted April 11th, 2017
Keywords Cholangiopancreatography, Magnetic Resonance; Cholangiopancreatography, Endoscopic Retrograde
Abbreviations BD-IPMN branch duct intaductalpapillary mucinous neoplasm; CT computed tomography; EUS endoscopic ultrasound; ERCP endoscopic retrograde cholangiopancreatography; MRCP magnetic resonance cholangiopancreatography; MRI magnetic resonance imaging
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DIAGNOSTIC MODALITIES

Magnetic Resonance Cholangiopancreatography/ Magnetic Resonance Imaging

MRCP can expose the pancreatic duct system and cystic or any other space-occupying lesions in detail. MRCP and MRI versus ERCP provide more sensitivity in detection of mural nodules. The sensitivity in diagnosis of IPMNs for MRI and MRCP are equal and significantly high (88%). This number for ERCP is 68% whereas CT scan has a sensitivity of 42%. With the mentioned number MRCP and its twin technique, MRI, can be considered as a standard modality for diagnosing IPMN including branch duct type [5]. Some authors believe that MRI in combination with MRCP have the potential to be the first option for optimal

management of BD-IPMN and more broadly all cases of IPMN [6].

MRI based on its superior contrast resolution for recognition of septum, nodules, and duct communication, can be a procedure of choice for evaluation of a pancreatic cyst, as has been suggested by a consensus of radiologists. On the other hand, for patients requiring frequent imaging for follow-up MRI may be a rational choice for avoiding radiation exposure. A recent study demonstrated that MRCP is the most reliable noninvasive modality to diagnose and follow-up BD-IPMN. MRCP is not only able to visualize the entire ductal system but also demonstrate communication between the cyst and the main pancreatic duct (MPD). These particular features of MRCP make it the gold standard for the assessment of BD-IPMN. MRCP is especially sensitive in providing a clear description of the morphology and assessment the growth over the time [7].

MRCP is routinely used in combination with contrast-enhanced MRI. MRCP is powerful in differentiation of BD-IPMN from main duct forms. In the setting of MRCP, accuracy in detection of main duct involvement is significantly high and this issue has a critical role for preoperative risk stratification of cancer. However MRCP is more accurate to identify small branch type lesions and multi focal branch disease. Data from MRCP gives a suitable orientation to surgeons for making decision over performing an effective and adequate resection. Some studies offered that MRCP have the potential to be the predominant imaging modality and in combination with other techniques makes it possible to characterize IPMN and further guide for designing the best treatment plan [5].

According to International consensus guidelines 2012, multidetector CT and MRCP are the most useful primary methods to identify the morphology, location, multiplicity, and communication with the MPD for diagnosis of BD-IPMN. Multiplicity and visualization of a connection to the MPD are reliable distinguishing features of BD-IPMN, although such a connection is not always observed. High risk stigmata of malignancy in a suspected BD-IPMN have been found by imaging include obstructive jaundice in a patient with cystic lesion of the head of the pancreas, enhancing solid component within cyst and main pancreatic duct >10 mm in size. If any of these features are detected in MRI/ MRCP of a patient who is clinically appropriate for operation surgery should be considered in this situation. On the other hand, if any of the following worrisome features present endoscopic ultrasound with or without fine needle aspiration (EUS±F NA) will be the next step. Worrisome features refer to presence of cyst >3 cm, thickened/enhancing cyst walls, main duct size 5-9 mm, non-enhancing mural nodule, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy. In the absence of worrisome and high risk features, patients will undergo close surveillance by CT/ MRI or EUS based on the largest cyst size found in basis imaging [8].

Both MRI and MRCP can detect cystic dilation of main pancreatic duct (MPD) because of their high contrast resolution. Moreover, using technical software three dimensional reconstructions can significantly improve the ability of the MRCP in detection of pathologies and gives more stronger diagnostic yields. These including post processing techniques such as multi planar reconstruction or maximum intensity projection. Multi planar images are practical tools to identification of the existence of connections between main and branch pancreatic ducts [9].

The strength of MRCP and CT in detection of the multifocality of the disease was documented 72% and 50% respectively. Moreover, MRCP was about two times stronger than CT in the detection of branch lesions. This paper also concluded that MRCP is a powerful tool for differentiation of various types of IPMN including BD-IPMN from mucinous cyst neoplasms. Reason is behind of its high resolution in demonstration of the ducts. As a result of high accuracy of MRCP in detection of involved main ducts it has a non-negligible role in risk assortment of cancer. By means of getting a precise picture of current situation of the disease, surgeons can easily choose the best surgical resection approach and have a clear and bright strategy [5, 8].

Endoscopic Ultrasound

If there are clear indications for surgery demonstrated on cross-sectional imaging that mentioned above additional evaluation with EUS ± FNA may not be necessary. The use of EUS±FNA varies widely throughout the world. EUS play a significant role in diagnosis, differentiation and classification of IPMNs. Its use in differentiation of benign and malignant cases is non-negligible. Combination of EUS and fine needle aspiration is helpful in getting cytology fluid for further evaluation [10]. EUS-FNA for cyst wall cytology, CEA, amylase, and occasionally k-ras mutation are also likely helpful in the diagnosis of pancreatic cysts beyond the radiologic imaging.

EUS finding in IPMN is partial or general dilation of main pancreatic duct that sometimes have an association with intraductal nodules. Dilation of the main pancreatic duct >5 mm without other causes of obstruction strongly suggests MD-IPMN [8]. Cyst formation that have communication with main pancreatic duct in situation that the diameter of main duct be lesser than 6 mm is consider as BD-IPMN. Sometimes there is more than one cyst in case of BD-IPMN and overall prevalence of multifocal forms is more in BD-IPMN. Pancreatic parenchymal atrophy is a common feature in MD and BD-IPMN [11].

In contrast to CT, EUS with or without FNA provide more strong chance for diagnosing pancreatic cystic neoplasms including BD-IPMN (P=0.002). On the other hand, EUS was superior to CT in case of detection of small cystic lesions (<3 cm) (P=0.003), equivalently, EUS was superior to MRI in large (>3 cm) lesions (P=0.030). Furthermore, EUS have precious role in depiction of pancreatic internal structures,

such as septum (P=0.004, versus CT and P=0.033 compared with MRI) and mural nodules (P=0.028, versus CT). Some other studies believe that depiction of ductal communication in MRI is dramatically better than CT [12].

Certain EUS findings including a main pancreatic duct more than 7 mm in MD-IPMN, cystic lesion >30 mm in BD-IPMN, and mural nodules >10 mm for both MD-IPMN and BD-IPMN are indicative of malignancy. Based on International consensus guidelines 2012 it is necessary for all BD-IPMNs with any specific "worrisome features" to have endoscopic ultrasound±fine needle aspiration. Presence of definite mural nodules, thickened cyst walls, intraductal mucin and cytology positive or suspicious for malignancy in EUS±FNA are suggestive of malignancy and should be considered for surgery. Differential diagnosis of mural nodule includes mucin that move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule in EUS include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue [8].

In cyst size issues investigations are controversial. Some studies found that the size is not a predictive factor for malignancy and it is not a reliable item for management decision. Some studies offer threshold of 3 cm for resection the cyst but some series shows that even in cyst with larger size it is possible to perform a successful follow up plan without unreasonable risk of malignancy happening and some other studies suggest that there is no safe lower size limit that can be reliable for excluding malignancy [10, 13].

The most suitable approach to evaluate IPMN more than 10 mm but less than 30 mm in size with no other concerning features is not clear. However some authors recommend additional evaluation with EUS-FNA if the patient is particularly concerned about malignancy. Following the patient with surveillance imaging is a reasonable approach when additional evaluation is not carried out. Surveillance imaging also is suggested for IPMN less than 10 mm in size [8].

All data recall the essential role of EUS in detection of malignancy and it can be helpful for determining the strategy of treatment [9]. Studies showed that EUS by itself have an accuracy only 51% in prediction of cyst based tumors and this issue reveals the importance of using EUS-guided fine needle aspiration(EUS-FNA)for diagnosis of pancreatic cysts.

In addition to EUS by itself, contrast enhanced-EUS (CE-EUS) is a powerful modality to distinguish mural nodules from mucinous clots, determining the probable mucosal fluid attached to mural nodules and provides sharper details of mural nodules height in versus of EUS alone. It is necessary to say that trials showed that the mural nodule height have been consider as a risk factor for malignant BD-IPMN, but the certain accuracy of CE-EUS in depiction of the height of mural nodules is still unclear [14, 15]. According to some investigations ability of CE-EUS in differentiation of malignant BD-IPMN was measured as 100% sensitivity, 86% specificity and accuracy of 94% [16].

Operator dependency, difficulty in sampling lesions smaller than 3 cm, non- diagnostic cytology or limited on-site cytological evaluation are limitations of EUS-FNA in BD-IPMN assessment and in setting of screening asymptomatic high risk cases some false positive results have been reported that cannot be ignored. EUS –FNA is an invasive procedure and accompanied by some complications including pancreatitis, abdominal pain or intracystic bleeding [17].

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) technically uses of X-ray to give a view of pancreatic ducts. It is composed of luminal endoscopy in combination with fluoroscopic imaging for using in diagnosis and treatment issues. Recently, as a consequence of decrease in diagnostic ERCP indications and developing of other modalities such as EUS and MRCP the general trend towards ERCP is reducing [18]. Aspirations of the duct contents or brushings to obtain cytology as well as therapeutic maneuvers to help clear the firm mucin from pancreatic duct can be performed by ERCP.

One of the special characteristics of ERCP is its ability to assess ductal communication in significant details but sometimes due to filling defect of contrast as a consequence of mucin plugging false diagnosis may happen. ERCP assessment of pancreatic duct indicates the existence of "fish eye" ampulla which is pathognomonic of IPMN. It is consists of a bulged ampulla which extrudes thick mucin visible with bare eyes. ERCP gives a direct eye on the site and lets the physician to get cytological samples and even can have therapeutic effects by its ability to evacuate of mucin from occluded pancreatic ducts [19].

For distinguishing mural nodules from mucin globs, MRCP is more sensitive than ERCP, because mucin has the same signal intensity as pancreatic fluid. On the other hand, in demonstrating the internal architecture of the main duct and extent of IPMN, MRCP is superior to ERCP. However in determining peripheral ductal abnormalities as well as ability to obtain tissue or perform therapeutic interventions, ERCP is superior to MRCP. The most sensitive tool to demonstrate mural nodules is endoscopic ultrasound.

Some small sized IPMN without "high risk stigmata" or "worrisome features" may be missed without cytology, therefore in some investigations ERCP has been used for cytological examination of ducts. Cytological evaluation by ERCP gives the ability to detect small size pancreatic duct malignancy, including malignant types of BD-IPMN. Some more studies with attention to this features of ERCP, may cause to establish some new indications in favor of early detection of small sized pancreatic cancers by "cytological examination mediated" ERCP [20]. Some new

investigations has been done on its role on routine follow up of BD-IPMN and they mentioned that routine ERCP is not necessary in BD-IPMN.

Needle-based Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a newly invented endoscopic method that allows imaging of the mucosal layer during endoscopy at a subcellular level of resolution. Therefore evaluation of changes in vascular architecture, connective tissue, and cellular components in the mucosa, as well as collecting real- time *in vivo* histological images or optical biopsies of the gastrointestinal mucosa during the endoscopy will be facilitated by this modality. CLE techniques using in pancreatobiliary assessment include probe-based confocal laser endomicroscopy (pCLE) in the bile duct and needle-based confocal laser endomicroscopy (nCLE) that uses a miniprobe passing through a 19G needle for pancreatic cystic tumors, pancreatic masses, and lymph nodes [21].

Inspection study which was the first multicenter study in this category, demonstrated that the presence of epithelial villous structures consisting of columnar epithelium and a vascular core based on nCLE is associated with pancreatic cystic neoplasm [intraductal papillary mucinous neoplasm (IPMN)]. Sensitivity, specificity, positive predictive value, and negative predictive value of nCLE for IPMN detection in this study were 59%, 100%, 100%, 50% respectively. These data concluded that while nCLE has a low sensitivity in detection of IPMN but is notable for its high specificity to demonstrate IPMN. The combination of the papillary projections feature, cytology and CEA level has been shown to have a sensitivity of 100% for the characterization of IPMN [22].

Pancreatic adenocarcinoma demonstrates dark cells that aggregate with pseudoglandular aspects and straight hyperdense elements more or less thick. Dense network of small vessels on a dark background is characteristic of neuroendocrine tumors in nCLE. All these nCLE features correlate with the histological structures of pancreatic cysts and tumors [22]. nCLE features of normal pancreas, IPMN and adenocarcinoma of pancreas are shown in Figures 1-4. These figures originate from Cellvizio.net.

Detection of malignant transformation within pancreatic cysts including BD-IPMN may be feasible with nCLE during an EUS examination. Furthermore avoiding unnecessary FNA, surgery or follow-up are the other advantages of nCLE in pancreatic cysts assessment but further investigations are needed to consider the role of this modality in BD-IPMN approach.

Positron-Emission Tomography

PET scanning has been performed for detecting malignancy in IPMN and in selecting patients for surgical resection. Pedrazzoli *et al*. examined the ability of PET scanning to detect malignancy in 162 patients with MD- or BD-IPMN. PET scanning compared with either histology (81 patients) or the results of surveillance (62 patients

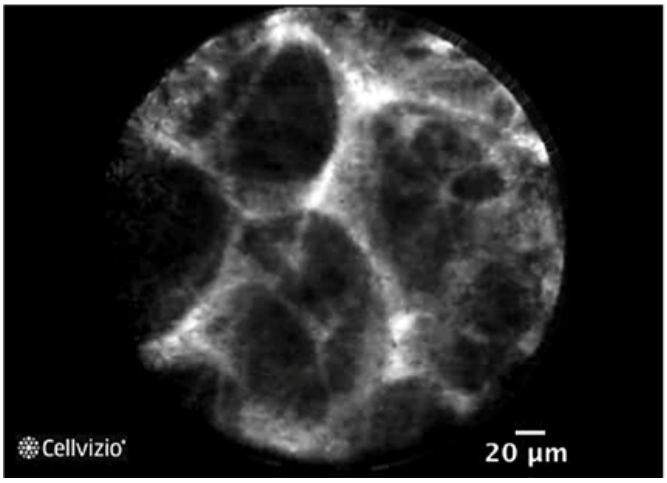

Figure 1. Non -malignant Ecc.

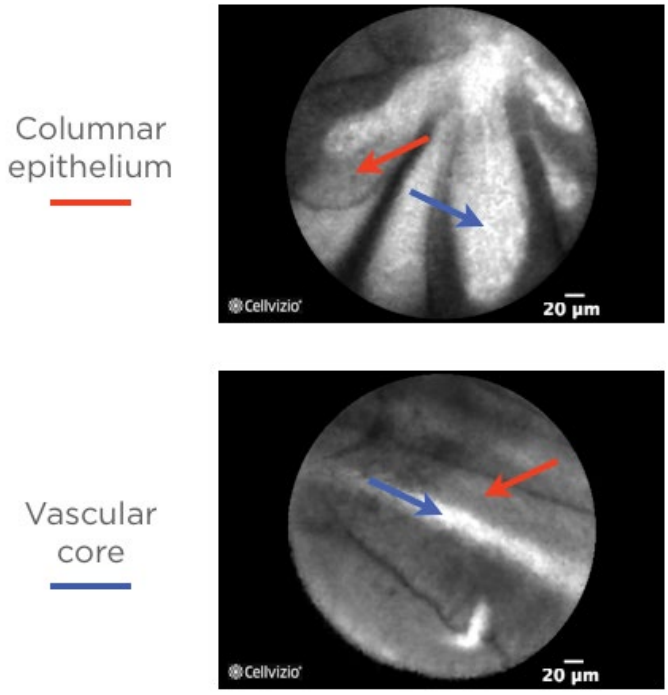

Figure 2. Intraductal papillary mucinous neoplasm (IPMN) without dysplasia.

median follow-up 21 months) in this study. Follow-up or histologic data of 19 patients were not available. The sensitivity and specificity for PET scanning were 83% and 100% respectively [23]. Some preliminary investigation suggests that 18F-fluorodeoxyglucose positron emission tomography may be helpful in detection of malignant forms of IPMNs [24]. PET scan can be considered as a potential tool with more significant role in diagnosis and management of IPMNs in the future.

Different Approaches in Various Guidelines and Recent Studies

The American Gastroenterological Association (AGA) guidelines on the evaluation and management of pancreatic cysts limited invasive evaluation to patients with concerning features including Cysts >3 cm in size, presence of solid components and dilated pancreatic duct.

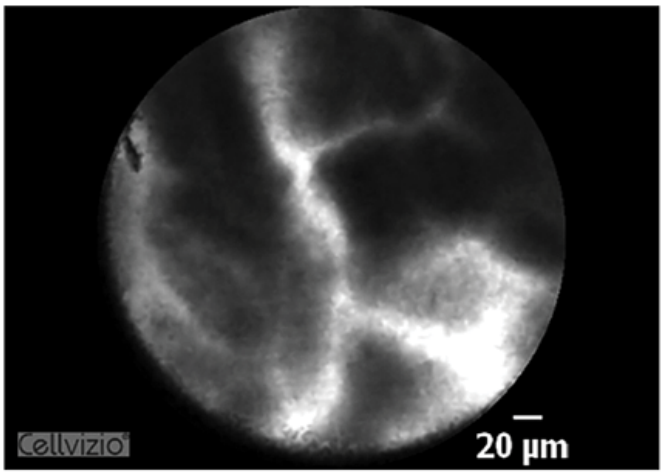

Figure 3. IPMN and high grade dysplasia**.**

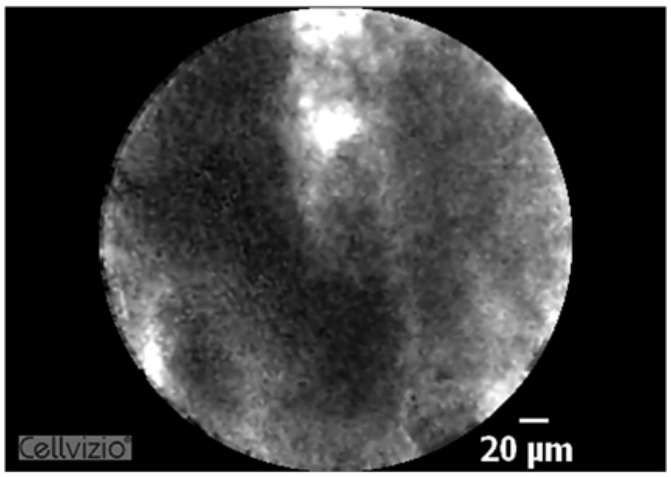

Figure 4. Solid pancreatic lesion adenocarcinoma.

Identification of any these features on cross sectional imaging necessitate further investigation with EUS ± FNA, whereas presence of more than one of three concerning features warrant surgical resection. It is important to remind that this guideline has not been validated in prospective studies and is based on low-quality evidence. According to AGA guidelines patients with pancreatic cysts without concerning features warranted surgical resection, should undergo surveillance with MRI every 1 to 2 years. However many malignant lesion may be missed by this recommendation [25].

Appropriate investigation of IPMN based on International consensus guidelines 2012 discussed above. According to these guidelines, absence of worrisome features on cross sectional imaging or resection criteria on MRI/MRCP and EUS and/or presence of inconclusive results in EUS in an asymptomatic patient with BD-IPMN indicate undergoing surveillance. There is inverse relationship between cyst size and interval of surveillance. Close surveillance alternating MRI with EUS every 3-6 month is suggested for cysts >3 cm whereas for cysts <1 cm CT or MRI in 2-3 years has been recommended. These guidelines noticed the data from Japanese studies which demonstrated increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. Since ability to detect early ductal carcinoma with imaging surveillance is unclear, surgery can be considered in young, fit patients with BD-IPMN cysts >2-3 cm who need for prolonged surveillance however it necessitates further study [8].

A recent study by Jin-Young Jang proposed a nomogram for predicting malignancy of BD- IPMNs using variables including pancreatic duct diameter, tumor size, mural nodule, and concentrations of the serum tumor markers (CEA and CA19-9). This study demonstrated very low risk of malignancy in patients with small cysts and no duct dilatation and mentioned patients without the risk factors detected in the consensus guidelines should undergo observation alone.

This nomogram can become a practical and useful tool in differentiation benign from malignant BD-IPMNs and determining risk of malignancy in individuals with BD-IPMN. Although it performed well on secondary validation, but further studies to validate in Western populations are required [4].

Girometti *et al*. studied on evolution of incidental branch-duct IPMN with MRCP. The rates of occurrence of imaging evolution and alert findings over the follow-up were assessed by image analysis in this investigation. Imaging evolution was described as any change in cysts number and/or size and/or appearance whereas alert findings were considered as worrisome features and/or high risk stigmata. They concluded that MRCP is the most useful noninvasive instrument to diagnose and follow-up presumed BD-IPMN. In this study evolution rate in incidental BD-IPMN mainly in terms of size increase assessed with MRCP was 44.4%, whereas the rate of occurrence of alert findings making further diagnostic evaluation was 8.3%. Definite malignancy or significant impact on patients' management was not demonstrated in further diagnostic evaluation of alert findings. They showed that clinical or baseline MRCP findings could not predict both types of changes. This study suggested that incidental BD-IPMN follow-up with MRCP should not be discontinued [7].

CONCLUSION

Despite vast studies about IPMNs there is a lack of data which exclusively pertain to BD-IPMN. Clinical sign and symptom of BD-IPMN are nonspecific and non-diagnostic. The sensitivity of MRI and MRCP in diagnosis of IPMN is equal and both of them are more sensitive than ERCP and CTscan. MRCP is necessary for pre operation stratification and has a precise role in designing suitable plan for surgery. It is essential for all BD-IPMNs with worrisome features to have endoscopic ultrasound with or without fine needle aspiration while doing FNA with EUS provides better diagnostic yields. MRCP and MRI are superior to ERCP in detection of mural nodules. In conclusion, the appropriate management of BD-IPMN, surgical resection or observation alone, depends on several factors including, age, concurrent comorbidities and the perceived risk of malignancy based on different imaging modalities. MRCP,

ERCP, EUS together with the novel technologies such as nCLE, PET scan have very important roles in the proper management of BD-IPMN, however further investigations are required to propose the best management of this entity.

Conflict of Interests

There is no conflict of interest in any fields of the study.

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