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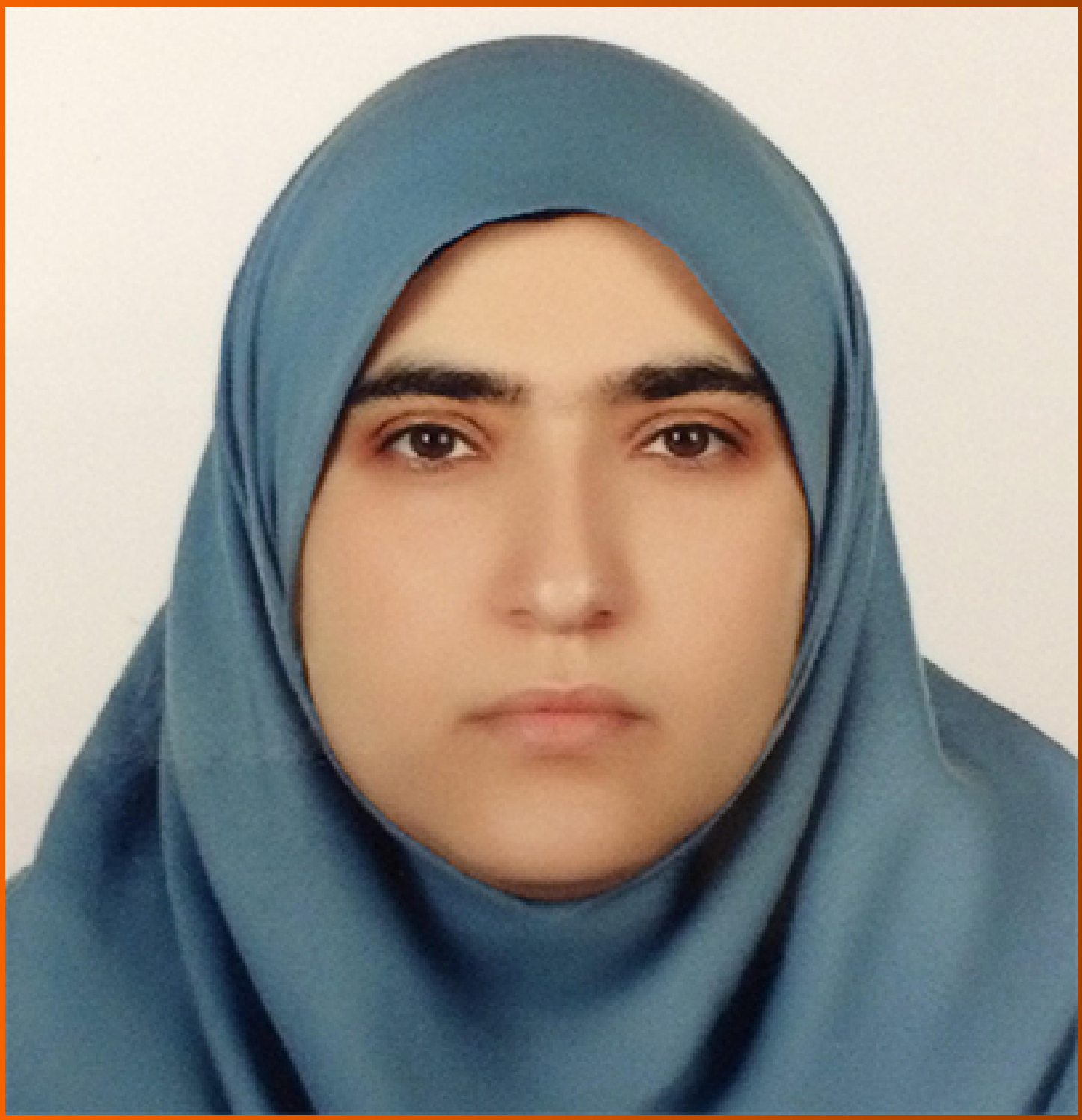

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REVIEW

Pancreatic intraductal papillary mucinous neoplasms: Current diagnosis and management

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Abstract

Intraductal papillary mucinous neoplasms (IPMNs) represent approximately 1% of all pancreatic neoplasms and 25% of cystic neoplasms. They are divided into three types: main duct-IPMN (MD-IPPMN), branch duct-IPMN (BD-IPMN), and mixed type-IPMN. In this review, diagnostics, including clinical presentation and radiological investigations, were described. Magnetic resonance imaging is the most useful for most IPMNs. Management depends on the type and radiological features of IPMNs. Surgery is recommended for MD-IPMN. For BD-IPMN, management involves surgery or surveillance depending on the tumor size, cyst growth rate, solid components, main duct dilatation, high-grade dysplasia in cytology, the presence of symptoms (jaundice, new-onset diabetes, pancreatitis), and CA 19.9 serum level. The patient's age and comorbidities should also be taken into consideration. Currently, there are different guidelines regarding the diagnosis and management of IPMNs. In this review, the following guidelines were presented: Sendai International Association of Pancreatology guidelines (2006), American Gastroenterological Association guidelines, revised international consensus Fukuoka guidelines (2012), revised international consensus Fukuoka guidelines (2017), and European evidence-based guidelines according to the European Study Group on Cystic Tumours of the Pancreas (2018). The Verona Evidence-Based Meeting 2020 was also presented and discussed.

Key Words: Pancreatic cyst; Pancreatic cystic neoplasm; Intraductal papillary mucinous neoplasm; Pancreatic cancer; Pancreatectomy; Guidelines

Core Tip: Intraductal papillary mucinous neoplasms (IPMNs) account about 1% of all pancreatic neoplasms and 25% of cystic neoplasms. We can distinguish three IPMN

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types: main duct-IPMN (MD-IPPMN), branch duct-IPMN (BD-IPMN), and mixed type-IPMN. Magnetic resonance imaging is the most useful approach for most IPMNs. Management depends on the type and radiological features of IPMNs. MD-IPMN is recommended for surgery. In BD-IPMN, management involves surgery or surveillance depending on the tumor size, cyst growth rate, solid components, main duct dilatation, high-grade dysplasia in cytology, the presence of symptoms (jaundice, new-onset diabetes, pancreatitis), and CA 19.9 serum level. The patient's age and comorbidities should also be taken into consideration. Currently, there are different guidelines regarding the diagnostics and management of IPMNs: Sendai International Association of Pancreatology guidelines (2006), American Gastroenterological Association guidelines, revised international consensus Fukuoka guidelines (2012), revised international consensus Fukuoka guidelines (2017), and European evidence-based guidelines based on the European Study Group on Cystic Tumors of the Pancreas (2018). The experts of Verona Evidence-Based Meeting 2020 determined the most important further directions regarding guidelines on IPMN management.

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INTRODUCTION

Pancreatic cystic neoplasms represent about 10%-13% of pancreatic cysts, 25% of cystic neoplasms and 1% of pancreatic carcinomas[1,2]. Pancreatic intraductal papillary mucinous neoplasms (IPMNs) are one of the two types of mucin-producing pancreatic cystic tumors (PCTs)[1,2]. According to World Health Organization, IPMNs are neoplasms which grow within the pancreatic ducts and produce mucin. They contain epithelial cells that can create papillary projections[2]. In 1982, Ohhashi *et al*[3], for the first time, reported four cases of mucin-producing pancreatic cancer. The term "intraductal papillary neoplasm" was introduced by Morohoshi[4] in a report of six cases in 1989. It should be added that numerous different terms were used for IPMNs before establishing the current nomenclature. The earlier names used were as follows: mucinous ductal ectasia, ductectatic mucinous cystadenoma and cystadenocarcinoma, intraductal mucin-hypersecreting neoplasm, intraductal papillary adenocarcinoma, intraductal mucin-producing tumor, and mucin-producing tumor[1].

At this time, the number of pancreatic IPMNs has significantly increased, and there are many reports on these tumors. The aim of this study is to review and present most of the current important literature regarding the etiopathogenesis, classification, diagnostics and treatment of pancreatic IPMNs.

ETIOLOGY AND PATHOGENESIS OF IPMNS

The etiology of pancreatic IPMNs is not clear. A main feature of many IPMNs is excessive mucin production. It has been reported that mucin 2 (MUC2) is procuded by most IPMNs, while there is no expression of mucin 1 (MUC1) in IPMNs, except of components of ductal cancer[5,6]. Adsay *et al*[6] noted that invasive ductal adenocarcinomas develop from intraepithelial neoplasms of the pancreas (PanINs) (5-y survival is less than 15%), whereas IPMNs are often associated with colloid carcinoma (5-y survival is better of more than 55%). It is known that an associated invasive carcinoma is reported in approximately 30% of patients with IPMN. Adsay *et al*[6] described an association of mentioned above pancreatic pathologies by investigating the expression of MUC1 and MUC2 glycoproteins as "aggressive" and "indolent" phenotypes in pancreatic carcinoma, respectively. In fact, MUC1 (mammary-type mucin) and MUC2 (intestinal-type mucin) have been reported as markers of "aggressive" and "indolent" phenotypes in pancreatic cancer, respectively. IPMN and colloid (mucinous noncystic) carcinoma form a distinct pathway of carcinogenesis in the pancreas, and MUC2 may

be the marker of this pathway. Furthermore, ordinary ductal carcinoma of the pancreas was found to lack expression of this marker but showed MUC1 expression instead[6]. In conclusion, the results of this study supported a dichotomial nature of the dysplasia-carcinoma in situ (CIS) sequence in the pancreas. Authors analyzed 2 routes leading to different types of invasive cancers. They noted that MUC2 is a marker of the "indolent" pathway (IPMN and colloid cancer), and MUC1 is a marker of the "aggressive" pathway (PanIN to ductal adenocarcinoma)[6].

In IPMNs, a classic "adenoma-carcinoma sequence" is observed. The duration of developing invasive carcinoma from low-grade dysplasia is approximately from 4 to 6 years. Various somatic mutations in the oncogenes KRAS and GNAS are reported in up to 90% of IPMNs. Other mutated genes are as follows: CDKN2A/p16, TP53, SMAD4, and less commonly STK11, BRAF, PIK3CA, PTEN. It has been noted that inactivated CDKN2A/p16, absent SMAD4 and mutation in TP53 are associated with progression from IPMN to carcinoma. They are almost exclusively reported in malignant IPMNs[7].

CLASSIFICATION OF IPMNS

IPMN is an exocrine neoplasm of the pancreas consisting of epithelial cells growing within the pancreatic ducts [main pancreatic duct (MPD) or its major branches and producing mucin[1]. There is no ovarian-type stroma in IPMNs in contrast to mucinous cystic neoplasms[2]. According to the revised international consensus Fukuoka guidelines (2017)[8], IPMNs are divided into the following three types: MD-IPMN, BD-IPMN, and MT-IPMN diagnosed in radiological/histological investigations. In MD-IPMN, MPD segmental or diffuse dilation of > 5 mm without other obstruction reasons is noted. Although MPD dilation of 5-9 mm is not an absolute indication for surgery, it is one of the "worrisome features". MPD diameter ≥ 10 mm is one of the "high-risk stigmata". BD-IPMNs are cystic lesions of the pancreas measuring > 5 mm which communicate with MPD. They need differential diagnosis with pseudocysts in patients followingacute pancreatitis. In MT-IPMN, the features of both MD-IPMN and BD-IPMN are present[7].

HISTOPATHOLOGY OF IPMNS

Histologically, pancreatic IPMNs are noninvasive epithelial neoplasms arising from cells which produce mucin located within the MPD or its branches[9]. According to the degree of cytological atypia and abnormal crowding of the epithelium, low-grade, intermediate-grade and high-grade dysplasia IPMNs are distinguished[10]. The four histopathological IPMN types are distinguished such as gastric type (49%-63%), intestinal type (18%-36%), pancreaticobiliary type (7%-18%), and oncocytic type (1%-8%). The gastric type is observed the most commonly. It is typically of low grade, rarely leading to cancer. Pancreatic cancer developing from this IPMN type is usually of the tubular type and is similar to ordinary pancreatic ductal adenocarcinoma. The intestinal type is reported in numerous MD-IPMNs. The pancreaticobiliary type is not well characterized and is uncommon. According to some authors, it is a high-grade dysplasia variation of the IPMN gastric type. Ductal and aggressive invasive cancer is commonly related to this IPMN type. The oncocytic type is the less frequent variant consisting of complex aborising papillae with delicate cores, oncocytic cells, and intraepithelial lumina formation. These lesions are uncommon and have limited invasion capability. Histological types correlate with the immunohistochemical phenotype of IPMN. This correlation was presented in Table 1[7,9].

DIAGNOSTICS OF IPMNS

Diagnostics of IPMNs involve analysis of clinical presentation, radiological imaging, and laboratory investigations, including biochemical and cytological tests.

Clinical presentation

The following clinical symptoms have been reported in patients with IPMNs: Epigastric discomfort or pain (70%-80%), loss of weight (20%-40%), nausea and vomiting (11%-21%), backache (10%), diabetes, and jaundice[5]. The mucin, which is

Table 1 Histological types and immunohistochemical profiles of intraductal papillary mucinous neoplasms[7,9]

Type	Percentage	Immunohistochemical profile			
		MUC1	MUC2	MUC5AC	MUC6
Gastric	49-63	(-)	(-)	(+)	(+)
Intestinal	18-36	(-)	(+)	(+)	(±)
Pancreatobiliary	7-18	(+)	(-)	(+)	(±)
Oncocytis	1-8	(+)	(-)	(±)	(+)

MUC: Mucin.

hyperproduced, can obstruct normal secretion in the pancreas, that is a reason of meals-related pain. In this case, a patient does not eat to avoid pain. In advanced tumors, loss of appetite is related to neoplastic cachexia. Jaundice is a consequence of obstruction of the common bile duct by viscid mucin, mural nodules, or direct compression due to the size of the IPMN. Persistent occlusion of the MPD with mucin can lead to exocrine and/or endocrine pancreatic insufficiency, and persistent hyperamylasemia[5]. Regarding clinical presentation, an association between IPMNs and recurrent acute pancreatitis (AP) should be emphasized. According to Venkatesh *et al* [10], the AP is reported in 12%-67% of IPMN patients. Both MD-IPMN and BD-IPMN may lead to AP, with a similar risk. AP in IPMN patients is usually mild and does not need treatment. There is no difference in AP occurence between benign and malignant IPMNs. AP occurs more frequently in IPMN patients compared to cancer patients, possibly because of obstruction of the MPD by mucin. It is important to remember the above mentioned association in patients with recurrent AP. Frequently, in patients following AP, pancreatic pseudocysts or fluid collections are diagnosed and IPMNs are less frequently considered in the differential diagnosis. In our opinion, oncological vigilance is very important in patients with pancreatic cystic lesions and recurrent pancreatitis in medical history because the prognosis and management of patients with IPMNs and pancreatic pseudocysts are different[10]. Jang *et al*[11] analyzed IPMN patients with AP or acute recurrent pancreatitis (ARP) (AP/ARP) treated in the period of 2000-2008 in a single tertiary referral center. IPMN-associated AP/ARP was noted 34 (7%) of 488 IPMN patients, and the MD/MT-IPMN more frequently was associated with AP/ARP compared to the BD-type (14% *vs* 5%; $P = 0.002$). The mild AP was diagnosed in analyzed patients. Histological findings of 24 surgically treated tumors were as follows: Adenomas ($n = 4$) (17%), borderline malignancies ($n = 17$) (71%), CIS ($n = 2$) (8%), and invasive carcinoma ($n = 1$) (4%). There was no AP/ARP recurrence in any patients during the follow-up period (median 52 mo, range 38-115 mo). The authors concluded that, though uncommon, AP/ARP could be an initial clinical IPMN manifestation, which is helpful in the diagnostic process[11].

Regarding ARP as a clinical IPMN manifestation, Bernardoni *et al*[12], in their preliminary report, assessed the efficacy of pancreatic sphincterotomy (PS) in patients with IPMN-associated ARP. A prerequisite for treatment was the fact that IPMN-associated ARP may lead to a lower quality of life and chronic pancreatitis. In IPMN manifested as AP, a higher cancer risk is reported. According to Fukuoka consensus [13], pancreatitis may be an indication for surgery despite of no signs of malignancy in radiological and cytological investigations[12,13]. However, pancreatic surgery is associated with an increased morbidity and mortality risk even when performed at high volume surgical centers. Higher surgical risks are reported in old patients with numerous comorbidities. According to the IPMN-associated AP pathophysiology, the hypothesis regarding the falicitated mucin outflow into the duodenum by PS has developed. According to this theory, reduction of intraductal pressure could lead to reduction of AP episodes[12]. The authors retrospectively analyzed patients with ARP and IPMN undergoing PS in 2010-2015. Patients were divided into two different groups: (1) MD/MT-IPMN; and (2) BD-IPMN with or without worrisome features/high-risk stigmata. In this study, complete, partial (reduction of pancreatitis episodes > 50%), and no response were reported in 11 (68.7%), 3 (18.7%), and 2 (12.5%) patients, respectively. In 1 (6.25%) patient, mild pancreatitis was observed following endoscopic retrograde cholangiopancreatography (ERCP). There was no cancer in resected patients. Additionally, during follow-up, there were no worrisome features/high-risk stigmata[12]. The authors concluded that PS was effective for reduction of the number of AP and it should be taking into condideration as a treatment option in

selected IPMN patients. It is important that systematic follow-up should be performed in this patients' group due to the malignant IPMN potential[12].

Apart from typical IPMN clinical presentation regarding abdominal symptoms and jaundice, skin lesions named pancreatic panniculitis have been reported. Yamashita *et al*[14] described a case of a 68-year-old man presenting pancreatic panniculitis on his trunk coexisted with IPMN-associated AP. A skin biopsy of the lesion histologically showed lobular panniculitis with characteristic "ghost cells" (pancreatic panniculitis). The authors concluded that clinicians should take into account IPMN in patients with in orderto avoid a missed or delayed diagnosis[14]. Similar cases of AP and IPMN-related panniculitis have also been reported by other authors[15,16]. Furthermore, IPMN-related panniculitis has been reported[17,18]. Therefore, we also recommend oncological vigilance in patients with panniculitis.

Infrequently, IPMN can form a fistula into the adjoining organs, including the stomach, duodenum, common bile duct, large and small bowel. The fistula may be related to benign IPMN (low-grade dysplasia). This fistula may occur as a consequence of mechanical penetration as a result of pressure by the mucin-filled ducts or due to inflammation or autodigestion by enzyme-rich fluids, or it could be a result of direct invasion due to malignancy, as in malignant IPMN (high-grade dysplasia)[5,9].

Some clinical symptoms, such as jaundice and new-onset diabetes, are more frequently associated with IPMN malignancy[5,19]. Additionally, according to Weisenauer *et al*[19], new-onset diabetes mellitus and jaundice suggest malignant IPMN. The authors noted that the absence of these features did not predict benign disease[19].

Imaging diagnostics of IPMNs

Currently, there are several different guidelines on diagnostic and therapeutic management in IPMN, including Sendai International consensus guidelines for the management of pancreatic IPMNs and mucinous cystic neoplasms according to the International Association of Pancreatology (IAP) (2006)[20], American Gastroenterological Association Institute guidelines on the diagnosis and management of asymptomatic neoplastic pancreatic cysts according to the American Gastroenterological Association (AGA) (2015)[21], revised international consensus Fukuoka guidelines for the management of IPMN of the pancreas (2012)[13], revised international consensus Fukuoka guidelines for the management of IPMN of the pancreas (2017)[8], and European evidence-based guidelines on pancreatic cystic neoplasms according to the European Study Group on Cystic Tumors of the Pancreas (2018)[22]. Diagnostic investigations are performed to select IPMN patients indicated for surgical resection. Therefore, diagnostic investigations should show alarming symptoms for malignant transformation in IPMN. As such, indications for surgery according to different guidelines should be known. They are presented in Table 2[5,8,13,20-22,41].

Computed tomography of the abdominal cavity

According to the most recent European guidelines for pancreatic cystic neoplasms (PCNs) (2018)[22], the accuracy of abdominal CT for identifying the specific PCN type is 40%-81%[22]. Multidetector row computed tomography (MDCT) for IPMN diagnosis should be performed according to a special standardized protocol[22]. Takeshita *et al*[23] evaluated predictive factors for discriminating benign from malignant pancreatic IPMN on MDCT. The study included 53 patients. Tumors were classified as MD-type (n = 7) and BD-type (n = 46). All MD-IPMNs weremalignant, while 8 of 46 BD-IPMNs were malignant, and 38 were benign. In additionn, MPD dilatation and mural nodules or large cystic diameter combined were significant risk factors of malignancy in BD-IPMN. According to the authors, MD-IPMN is strongly associated with malignancy[24]. Nakagawa *et al*[24] retrospectively evaluated the utylity of MDCT with multiplanar reformations and curved planar reformations in diagnosis of protruding lesions in IPMNs compared to single-detector CT (SDCT) and endoscopic ultrasonography (EUS). This study showed that MDCT was more useful than SDCT and similar to EUS in diagnosis ofprotruding lesions in IPMNs[24]. Tan *et al*[25] also retrospectively evaluated the imaging features of IPMNs in MDCT. Comparison with the pathological diagnosis revealed that the sensitivity, specificity, and accuracy of MDCT in assessing the IPMN were 100%, 87.5% and 95%, respectively. Thus, MDCT can be used to predict the IPMN malignancy[26]. Murayama *et al*[26], compared CT and MRI in assessment of IPMN malignancy. There was a statistical difference in MPD diameter (P = 0.017) and intraductal volume (P = 0.0013) inadenoma, CIS, and invasive cancer. This study showed that intraductal volume (≥ 10 cm) was helpful in the malignant IPMN diagnosis[26].

Table 2 Indications for surgery in intraductal papillary mucinous neoplasms according to the International, European and American Gastroenterological Association guidelines[5,8,13,20-22,41]

Guidelines	Indications for surgery
IAP (2006)	Symptoms; Cyst size ≥ 3 cm; Mural nodule; MPD ≥ 5 mm; Positive cytology
AGA (2015)	High risk features: Cyst size ≥ 3 cm; Presence of solid component; Dilated MPD
	HGD or cancer on cytology
IAP (2017)	High risk stigmata: Jaundice; Enhancing mural nodule ≥ 5 mm; MPD ≥ 10 mm
	HGD or cancer on cytology
	Worrisome features: Cyst size ≥ 3 cm; Acute pancreatitis (due to IPMN)
	Enhancing mural nodule ≥ 5 mm; Thickened and enhancing cyst wall
	MPD dilation 5-9 mm; Abrupt change of MPD caliber with distal pancreatic atrophy; Presence of lymphadenopathy; Elevated serum CA 19-9; Cyst growth rate > 5 mm/2 yr
European (2018)	Absolute indications: Jaundice; Enhancing mural nodule ≥ 5 mm; MPD ≥ 10 mm; HGD or cancer on cytology; Solid mass
	Relative indications: Cyst size ≥ 4 cm; Enhancing mural nodule ≥ 5 mm/years; Acute pancreatitis (due to IPMN); New onset of diabetes; Rapidly increasing cyst size; Elevated serum levels of CA19-9

IPMN: Intraductal papillary mucinous neoplasm; IAP: International Association of Pancreatology; AGA: American Gastroenterological Association; MPD: Main pancreatic duct; HGD: High grade dysplasia.

Monnings *et al*[27] analyzed preoperative CT scans in IPMN patients. Benign (bIPMN; n = 28) and malignant (mIPMN; n = 19) tumors were compared. The MPD diameter was greater in patients with mIPMN (P < 0.0001). Obstruction of the bile duct, solid tumor components, contrast enhancement in walls of the cyst, peripancreatic lymph nodes, and abrupt MPD diameter changes were observed in more mIPMN patients (P < 0.01). In addition, in mIPMN, the CT cyst density was higher (P = 0.0063). The summary diagnostic accuracy was higher than all single CT parameters [27].

Apart from the numerous above mentioned benefits, CT also has a disadvantage, which is most important in IPMN patients requiring systematic control imaging diagnostics. It has been reported that repeated exposure to ionizing radiation following CT increases the cancer risk[22,28]. Sodicson *et al*[28] estimated the cumulative radiation exposure and lifetime attributable risk (LAR) of radiation-induced cancer from CT scanning of adult patients at a tertiary care academic medical center. The analysis showed that 33% of patients had ≥ 5 lifetime CT investigations, and 5% had 22-132 examinations. Cumulative effective doses > 100 mSv in 15%, and 250-1375 mSv in 4% of patients, respectively, were reported. In 7 % of patients, LAR > 1% was noted. It should be added that assigned effective doses per CT examination are as follows: for CT of the abdomen (without pelvis), 7.5 mSv, and for CT of the abdomen and pelvis, 15 mSv[28].

MRI and magnetic resonance cholangiopancreatography

According to European guidelines for PCNs[22], the accuracy of MRI/magnetic resonance cholangiopancreatography (MRCP) for identifying the special PCN type is 40%-95%. These guidelines recommend MRI as the preferred method for the investigation of patients with PCN. The higher sensivity of MRI/MRCP compared to CT for detection of communication between a PCN and the pancreatic ducts and presence of mural nodules or internal septations has been noted. MRI/MRCP is also good in the differential diagnosis of single and multiple PCNs, including multifocal BD-IPMN. Moreover, IPMN patients frequently require long-life control investigations, and MRI is less invasive than CT[24]. According to the same guidelines, MDCT is helpful for diagnosis of calcification, tumor staging assessment, or for diagnosing postoperative recurrent disease[22].

Min *et al*[29] retrospectively analyzedpatients undergoing surgery for IPMN followingpreoperative CT and MRI in 2009-2019. There were 88 (50.3%) malignant IPMNs in this study. All 3 high-risk stigmata (MPD ≥ 10 mm, mural nodule ≥ 5 mm, and obstructive jaundice) and 2 worrisome features (MPD 5-9 mm and increased level of CA 19.9) were related to malignant IPMN on CT and MRI (P < 0.05). A mural nodule < 5 mm on MRI was also related to malignant IPMN (P < 0.01). This study showed that CT and MRI were comparable for diagnosis of high risk stigmata (73.7% *vs* 75.4%; P =

0.505). In addition MRI was superior to CT for diagnosis of mural nodules, and similar to CT for differentiation ofmalignant from benign IPMNs[29].

Liu *et al*[30], in a meta-analysis, assessed the diagnostic properties of CT, PET/CT, MRI/MRCP, DWI, and EUS in differential IPMN diagnosis (benign *vs* malignant tumors). Twenty eight studies were included. This study showed the highest diagnostic accuracy results for PET/CT, and the use of MRI/MRCP, PET/CT was recommended as a first-line investigation in the diagnosis of malignant IPMN, and DWI, EUS and CT were additional for MRI/MRCP in IPMN diagnosis[30].

Jeon *et al*[31] investigated the MRI utility to predict the malignant IPMN potential. In this study, enhancing mural nodule size ≥ 5 mm, MPD ≥ 10 mm / MPD of 5-9 mm, and MPD abrupt changes significantly predicted to malignant IPMNs ($P < 0.05$). In multivariate analysis, enhancing mural nodules ≥ 5 mm, MPDs ≥ 10 mm or MPDs of 5-9 mm, larger entropy, smaller compactness were significant predictors for malignant IPMNs ($P < 0.05$)[31].

Boraschi *et al*[32] retrospectively in their retrospective study, showed the MRI utility in the diagnosis of worrisome features and high-risk stigmata in patients with BD-IPMNs during 10 years of observation from the tumor diagnosis[32].

Endoscopic ultrasound

According to European guidelines[22], EUS is recommended as additional to other radiological investigations. It is helpful for diagnosing PCN indicated for surgery. Similar to MRI and CT, EUS is not perfect in diagnosis of the exact PCN type of EUS is recommended in patients with PCNs with concern clinical or radiological features[22].

Contrast harmonic enhanced EUS (CH-EUS) is recommended for assessment of mural nodules. CH-EUS is also useful in assessment of presence of vessels and septations within the cyst. Hyperenhancement of a mural nodule, solid mass, or septations on CH-EUS predict malignancy, that is indication for EUS-fine needle aspiration (FNA) of the tumor[22].

Choi *et al*[33] compared EUS, CT and MR in the diagnosis of IPMN malignant transformation. All compared investigations were similar in this analysis. In the multivariable analysis, enhanced solid components on contrast-enhanced CT and MRI and mural nodules on EUS, MPD diameters ≥ 10 mm, MPD diameters of 5-9 mm and thickened septa or walls were significant ($P < 0.05$). Thus, the diagnostic performance of CT, MRI, and EUS for predictiion of malignant IPMNs was comparable[33].

The diagnostic accuracy of EUS increases if biopsy is performed and pancreatic cyst fluid is collected for analysis during EUS. EUS-FNA increases diagnostic accuracy for differentail diagnosis of mucinous from nonmucinous PCN and malignant from benign PCN in patients in whom CT or MRI are unclear. A combined analysis of cyst fluid CEA, lipase levels, and cytology has the highest accuracy for differential diagnosis of mucinous from nonmucinous PCNs. It is important that EUS-FNA is recommended only when the results can modify management and EUS-FNA should not be performed if the diagnosis is already made using radiological investigations and in patients with clear indications for surgical treatment. Relative contraindications for this investigation are as follows: A distance of > 10 mm between the cyst and the transducer, a high hemorrhage risk, and the use of dual antiplatelet drugs[22]. Assessment of cyst fluid CEA, combined with cytology, or KRAS/GNAS mutation analyses may be considered for differentiating an IPMN or MCN from other PCNs[22].

Mc Carty *et al*[34] published a systematic review and meta-analysis including 6 studies (785 tumors) to asses the diagnostic utility of K-ras and G-nas mutations in EUS-acquired pancreatic cyst fluid for the diagnosis of IPMNs and mucinous cystic lesions. It should be added that molecular cyst fluid diagnostics are not yet a standard. There was a significantly higher accuracy of combined K-ras + G-nas compared to K-ras alone and G-nas alone in the differential diagnosis ($P < 0.001$). The pooled sensitivity, specificity, and diagnostic accuracy of K-ras + G-nas mutations in the IPMN diagnosis were 94%, 91% and 97%, respectively. They were significantly higher compared to CEA alone (all $P < 0.001$)[34].

Kadayifci *et al*[35] investigated the value of GNAS investigation in addition to KRAS and CEA tests of pancreatic cystic fluid (PCF) for the IPMN diagnosis. There were 108 IPMN and 89 non-IPMN patients in the analyzed group. GNAS was noted in 51 (47.2%) IPMN patients, and a KRAS mutation was noted in 42 (82.3%) patients. The diagnostic accuracy increased from 76.6% to 79.1% ($P > 0.05$), when GNAS to KRAS was added and from 66.4% to 80.7% ($P < 0.05$) when GNAS to CEA was added. It should be noted that the diagnostic accuracy of the combined all tests was significantly higher compared to all single investigations ($P < 0.05$)[35].

Lee *et al*[36] published a meta-analysis to analyze KRAS and GNAS mutations in pancreatic cystic lesions. In this study, KRAS and GNAS mutations were more common in IPMNs compared to mucinous and serous cystic neoplasms, respectively. KRAS and GNAS mutations were frequently reported in the gastric ($P < 0.001$) and intestinal ($P < 0.001$) types, respectively. KRAS mutation was not common in high-grade dysplasia IPMNs ($P = 0.032$). This meta-analysis confirmed that KRAS and GNAS mutations are useful for diagnostic tools for IPMN[36].

Gillis *et al*[37], in their meta-analysis, noted 42% sensitivity and 99% specificity of PCF cytological analysis for differential diagnosis of mucinous *vs* nonmucinous PCNs [22]. According to most authors, a cyst fluid CEA cutoff level of ≥ 192 ng/mL can differentiate mucinous cysts from nonmucinous cysts, with a sensitivity of 52%-78% and specificity of 63%-91%[22].

Indications for EUS-FNA are different depending on International Consensus Guidelines (ICG), AGA, and European guidelines. According to ICG, this investigation is indicated in patients with pancreatitis, tumor diameter > 30 mm, thickened or enhanced wall of the cyst, MPD 5-9 mm, nonenhancing mural nodules, abrupt tapering of the pancreatic duct and atrophy of the distal tail. AGA recommends EUS-FNA in the presence of two of the following risk factors: cyst diameter > 30 mm, the presence of a solid component in the cyst, and MPD dilatation. The European guidelines recommend the use of EUS as part of a multimodality diagnostic assessment[38,39].

ERCP and/or pancreatoscopy

The role of ERCP in IPMN diagnostics is limited. According to European guidelines [22], pancreatoscopy may be used in selected patients to assess the MD-IPMN location and extent and can help to differentiate MD-IPMN from chronic pancreatitis. The diagnostic accuracy of pancreatoscopy was higher in MD-IPMN (88%) compared to BD-IPMN (67%). Intraoperative MPD pancreatoscopy made with frozen sections of intraductal biopsies may be used in assessment of the IPMN extent and MPD involvement, which is important for surgeons' decisions regarding the extent of surgical resection[22].

Blood tests

The role of blood tests in IPMN diagnostics is also limited. According to current guidelines on IPMNs[22], molecular blood tests are not used in PCNs diagnostics. Only serum cancer antigen CA 19.9 can be useful in IPMN in patients with malignant transformation suspected[22].

MANAGEMENT OF IPMNS

Indications for surgery

Management of IPMNs is still controversial because of different recommendations of the ICG, AGA, and European guidelines. The earliest (2006) Sendai ICG guidelines were the most restrictive. In 2006, Tanaka *et al*[20] recommended resecting all MD- and MT-IPMNs as long as the patient is a good candidate for surgery. Patients with BD-IPMNs, with no symptoms, require surgery not only to relief the signs but also due to a n increased risk of malignant transformation. Moreover, according to these guidelines, BD IPMNs > 30 mm in diameter and without MPD dilation or mural nodules should be assessed if all BD-IPMNs > 30 mm in diameter require surgery immediately. The Sendai recommendations have resulted in a high rate of "unnecessary" pancreatic surgeries. This is important because pancreatectomy is a complex procedure associated with relatively high morbidity and mortality rates[38]. The original Sendai group published revised ICG, commonly known as the Fukuoka guidelines in 2012. According to the IAP Fukuoka 2012 guidelines, revised in 2017, surgery is strongly recommended for all MD-IPMNs with a MPD of diameter > 10 mm or with "high-risk stigmata" (HR), such as an enhancing solid component or jaundice. Dilatation of the MPD 5-9 mm is considered a "worrisome feature," and it is not recommended for immediate resection but requiring further assessment using EUS[8, 13]. In 2015, AGA recommended surgical treatment for patients, with no symptoms, only in the presence of two of three "concerning features" (presence of nodule, diameter > 30 m, or duct dilation) and malignant transformation in EUS-FNA[21].

Authors of the European guidelines[22] recommended surgery in IPMNs with jaundice, an enhancing mural nodule (≥ 5 mm) or a solid component, positive cytology, or MPD diameter ≥ 10 mm. Surgical management was also recommended for

IPMNs with MPD dilatation 5-9.9 mm, cystic growth rate ≥ 5 mm/year, elevated serum CA 19.9 concentration (> 37 U/mL), signs, enhancing mural nodules, and IPMNs > 40 mm regardless of the presence of other high-risk factors[22]. In BD-IPMNs, jaundice, high-grade dysplasia or cancer in cytology, a contrast-enhancing mural nodule (≥ 5 mm) or solid mass are absolute indications for surgery. The relative indications for surgery are the following: Growth rate ≥ 5 mm/year, elevated serum CA 19.9 concentration (in the absence of jaundice), MPD diameter 5-9.9 mm, IPMN size ≥ 40 mm, clinical manifestation (new-onset diabetes mellitus or AP), and contrast-enhancing mural nodules[22].

In conclusion, according to all current guidelines, surgical treatment is recommended in all IPMNs involving the MPD, but there is still no consensus regarding MPD dilation. In the absence of other "high-risk stigmata", MPD dilatation alone is considered as a risk of misdiagnosis and possible overtreatment. Therefore, some authors suggested radiologic surveillance in patients with no symptoms and with "worrisome" MPD dilatation (5-9 mm) and without other HR stigmata[40]. All guidelines regarding current management in IPMN patients are presented in Table 3 [5,8,13,20-22,41].

Extent of surgical resection

According to Sendai guidelines[21], pancreatectomy with lymphadenectomy is necessary when invasive cancer is suspected. The type and extent of surgery depend on the IPMN location and extent[22]. The pancreatic head is the most frequent IPMN location. Therefore, pancreaticoduodenectomy (PD) is recommended in IPMNs located within the pancreatic head, uncinate process, and neck. Distal pancreatectomy (DP) is indicated for IPMNs located within the pancreatic body and tail. Total pancreatectomy (TP) is performed in exceptional cases when IPMN diffusely involves the whole pancreas or when a proximal IPMN extends through the distal pancreas. It is associated with the long-term consequences of TP, such as exocrine and endocrine pancreatic insufficiency requiring supplementation of pancreatic enzymes and diabetes treatment with insulin use. In each partial pancreatic resection, an assessment of the margin by frozen section is needed to confirm R0 resection with negative margins, and the resection should be extended in cases with cancer-positive surgical margins[5].

According to the revised Fukuoka guidelines[8], PD, DP, or TP according to the IPMN location and extent with lymphadenectomy should be the standard surgical treatment. Limited resections or even focal nonanatomic resections (excision, enucleation, uncinatectomy) can be performed in BD-IPMN not suspected for invasive cancer[8]. The authors added that nonanatomic resections could be associated with infrequent but possible mucin leakage followed by peritoneal pseudomyxoma, a higher risk of postoperative pancreatic fistula and a risk of neoplasm recurrence. Standard pancreatectomy and lymphadenectomy should be performed if the cancer possibility is present[8]. We recommend using the European guidelines in decision making regarding the extent of IPMN surgery. According to the European guidelines [22], PD with frozen section investigations of the resection margins is recommended for patients with MPD dilatation comprising the entire pancreas. TP can be taken into consideration in patients with mural nodules within the MPD, and a higher cancer risk (familial pancreatic cancer). For BD-IPMNs, the authors recommend oncological resection with standard lymphadenectomy. It should be emphasized that parenchyma-sparing pancreatectomy is not an oncological procedure that can be performed only in lesions with a very low malignancy probability-for example, in patients without risk factors strongly wishing to be surgically treated. Due to a high malignancy risk, oncologic resection including standard lymphadenectomy is the recommended for IPMN with an absolute indication for resection. In multifocal BD-IPMN, each tumor should be assessed individually for the presence of malignancy-associated features. Patients with IPMNs with no concerning features can be observed[22].

Surveillance in IPMN patients

Patients with IPMNs lacking HRS/absolute indications should undergo nonoperative management. The surveillance strategies according to different guidelines are presented in Table 4[5,8,13,20-22,41].

According to the revised Fukuoka guidelines, surveillance is determined by IPMN diameter. The revised guidelines are more restrictive compared to the Fukuoka (2012) and Sendai guidelines (2006) and recommend initial surveillance performed at a shorter interval (within 6 mo for cysts < 20 mm and within 3-6 mo for cysts 2-3 cm). Following initial risk stratification, cysts < 10 mm should be radiologically monitored every 2 years in cysts with no changes. Cysts 10-20 mm should also be controlled

Table 3 Management of intraductal papillary mucinous neoplasm patients regarding indications for surgery according to the International, European and American Gastroenterological Association guidelines[5,8,13,20-22,41]

Guidelines	Management
IAP (2006)	Indications: Surgery
AGA (2015)	Indications: Surgery
IAP (2017)	High risk stigmata: Surgery
	Worrisome features: Surgery versus close surveillance based on: Patients' age/comorbidities: More aggressive management (surgery) in young patients
	EUS findings: Surgery indicated in clear MPD involvement and/or high-risk features
European (2018)	Absolute indications: Surgery
	Relative indications: Surgery according to criteria count, depending on comorbidities
	In fit patients: surgery for 1 criterion
	In patients with significant comorbidities: surgery for 2 criteria

IAP: International Association of Pancreatology; AGA: American Gastroenterological Association; EUS: Endoscopic ultrasonography; MPD: Main pancreatic duct.

Table 4 Surveillance in intraductal papillary mucinous neoplasm patients regarding indications for surgery according to the International, European and American Gastroenterological Association guidelines[5,8,13,20-22,41]

Guidelines	Indications	Investigations	Algorithm of follow-up
IAP (2006)	BD-IPMNs ≤ 30 mm; Without: Symptoms, mural nodules, positive cytology	MRI/MRCP or CT	Size ≤ 20 mm: every 6-12 mo; Size 20-30 mm: every 3-6 mo; The interval can be longer after 2 yr without changes
AGA (2015)	BD-IPMNs ≤ 30 mm; Without: Solid component, dilated MPD, HGD/cancer	MRI	Years 1, 2, 5 from initial diagnosis; It can be considered to discontinue; If there is no changes after years
IAP (2017)	No HRS/WF	MRI/MRCP, CT	Size < 10 mm: At 6 mo from diagnosis every 2 yr (if no change)
	No HRS/WF	MRI/MRCP, CT	Size 10-20 mm: At 6 mo from diagnosis yearly per 2 yr
	No HRS/WF	MRI/MRCP, EUS	Size 20-30 mm: EUS in 3-6 mo, yearly EUS or MRI
	No HRS, WF present and size < 30 mm	MRI/MRCPEUS	Every 3-6 mo EUS or MRI
European (2018)	No AI	MRI/MRCP or EUS, CA 19.9	Every 6 mo for the first year; Yearly after first year
	No AI, 1 RI in patient, with comorbidities	MRI/MRCP or EUS, CA 19.9	Every 6 mo

IPMN: Intraductal papillary mucinous neoplasm; IAP: International Association of Pancreatology; AGA: American Gastroenterological Association, MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; MPD: Main pancreatic duct; HGD: High grade dysplasia; EUS: Endoscopic ultrasonography; HRS: High risk stigmata; WF: Worrisome features; AI: Absolute indications for surgery; RI: Relative indications for surgery.

radiologically every 2 years, EUS or MRI should be performed every 1 year in cysts 20-30 mm. A diameter change alone (≥ 5 mm growth in 2 years), in addition to the presence of any worrisome features, is sufficient to recommend systematic EUS[8,13,20,41].

The AGA guidelines[21] recommend surveillance for patients with BD-IPMNs < 30 mm, with no a solid component, dilated MPD, HGD or cancer in cytologic findings. In these patients, MRI should be performed in years 1, 2, and 5 from initial diagnosis. If no significant change occurs, surveillance discontinuation should be considered. Other patients should be referred to surgery[8,21].

The authors for the European guidelines recommend a 6-mo follow-up (using MRI/MRCP and/or EUS and serum CA 19.9) in the first year and then yearly follow-up, in patients with a suspected IPMN that does not meet the indication for surgery.

The guidelines recommend to continue observation as long as the patient remains surgically fit[8,22,39].

Follow-up after surgery

According to the revised Fukuoka guidelines[8], all IPMN patients, including those with noninvasive IPMNs with negative surgical margins, need follow-up after surgery to diagnose a new IPMN requiring surgery or pancreatic cancer. Tanaka *et al*[8] recommend continuing surveillance as long as the patient remains fit. In patients with higher risks, such as a family history of pancreatic cancer, HGD in surgical margins, and nonintestinal IPMN histological type, radiological investigations at least twice a year are recommended, and in others investigations every 6-12 mo should be performed. The follow-up of invasive IPMN should be the same as in pancreatic cancer [8].

The European guidelines are similar, and according to them[22], lifelong follow-up is recommended after IPMN resection as long as the patient is fit for surgery. Patients with IPMN-associated invasive cancer should be followed up in the same manner as those with resected pancreatic cancer. In HGD IPMN and MD-IPMN, follow-up every 6 mo for the first 2 years, followed by yearly surveillance is recommended. LGD IPMN should be observed in the same manner as nonresected IPMN. Patients with IPMN in the remnant pancreas with no HGD or MD-IPMN should be observed as nonresected BD-IPMN. In a postoperative observation, MRI or EUS are recommended[22].

The AGA guidelines are very liberal. The authors recommend postoperative surveillance only for patients following surgery due to invasive IPMN. According to the AGA guidelines, patients with invasive cancer or dysplasia in the cyst after surgery should undergo MRI every 2 years. Moreover, the AGA did not recommend routine follow-up of IPMNs with no HGD or malignancy in the surgical specimen[21].

The clinical utility of the current guidelines regarding the management of IPMNs

Hsiao *et al*[42] evaluated the utility of the 2006 Sendai and 2012 Fukuoka guidelines in the differential diagnosis malignant and benign IPMNs. The study included 138 IPMN patients operated on between January 2000 and March 2015. Patients were "Sendai positive" if the tumor diameter was ≥ 30 mm, with no symptoms, with mural nodules or a thickened wall, or with a dilated MPD of ≥ 6 mm. Patients without above mentioned criteria were classified as "Sendai negative". Patients were characterized as "Fukuoka high risk" in the presence of: obstructive jaundice, or enhancing solid component, or MPD of ≥ 10 mm. "Fukuoka worrisome" were IPMNs with the presence of any worrisome features (pancreatitis, a tumor diamater of ≥ 30 mm, a thickened/enhancing cyst wall, nonenhancing mural nodules, an abrupt MPD diamater change with distal pancreatic atrophy, and an MPD of 5-9 mm). The positive predictive value (PPV) and negative predictive value (NPV) of the Sendai and Fukuoka guidelines for HGD/IC were 35.1%, 43.3%, 100%, and 85.4%, respectively. According to the multivariate analysis, jaundice, tumors of ≥ 30 mm, presence of mural nodules, and age < 65 years were associated with HGD/invasive cancer in IPMN patients. There was a better NPV in the Sendai guidelines, but a better PPV in the Fukuoka guidelines. In the authors' opinion, a more aggressive management in patients with Fukuoka worrisome features couled be considered. The study showed that IPMNs of ≥ 30 mm, but not pancreatitis, are associated with malignancy[42].

Pérez-Cuadrado-Robles *et al*[43] assessed the accuracy of the European guidelines in BD-IPMN patients indicated for surgery in a multicenter, observational, retrospective study including 91 patients with absolute (n = 21), relative (n = 60), or no formal indications (n = 10) for surgery. There were 60 patients with one (n = 35) or ≥ 2 relative indications (n = 25) for surgery in this study. The global advanced tumor and invasive cancer rates were 40% and 13.3%, respectively. There were not risk factors for GHD or invasive cancer. A lower risk of invasive cancer was reported in patients with one relative indication compared to patients with ≥ 2 relative indications (5.7% *vs* 24%, respectively; P = 0.048). The advanced IPMN incidences were similar in the compared groups (37.1% *vs* 44%; P = 0.593)[43].

Jan *et al*[44] also validated the European guidelines for the management of IPMNs. The study included 158 patients with resected IPMNs between January 1994 and December 2016. All patients were stratified into three groups according to the European guidelines: Absolute, relative indications, and conservative approach. The missed rate for HGD/IC by the European guidelines was 1.9% (3 of 158). The sensitivity, specificity, positive and negative predictive values, and accuracy of the absolute or relative indications for resecting IPMN according to these criteria were 94.1%, 28.0%, 38.4%, 90.9%, and 49.4%, respectively. Jaundice, enhancing mural nodules < 5 mm, cyst diameter > 40 mm, elevated serum CA 19.9 concentration, new-

onset diabetes, and MPD dilation were associated with HGD/IC. Thus, the missed rate for HGD/IC was low using the European guidelines. Increased serum CA 19.9 and new-onset diabetes in European recommendations were verified as indications for the surgical resection of IPMNs[44].

Correa-Gallego *et al*[45] analyzed two independent nomograms to predict the findings of adenoma, high-grade dysplasia (HGD-CIS), and invasive carcinoma separately in both MD- and BD-IPMN. This study involved 219 patients including 56% of BD-IPMN in resected specimens. The significantly higher proportion of HGD-CIS was reported in MD-IPMN (33%) compared to BD-IPMN (15%) ($P = 0.003$). Invasive cancer was significantly more frequent in MD-IPMNs (41%) compared to BD-IPMNs (15%) ($P < 0.001$). In addition patient sex, history of prior malignancy, presence of a solid component, and weight loss were significantly associated with the ordinal outcome for MD-IPMN patients and were included in the nomogram (concordance index 0.74). For BD-IPMN patients, weight loss, solid component, and lesion diameter were associated with the outcome (concordance index 0.74)[45].

Capurso *et al*[46] investigated patient- and cyst-related factors associated with progression into WF or HRS categories of BD-IPMNs. This study included 540 patients diagnosed from 2009 to 2018 with at least 12 mo of surveillance until February 28, 2020. The revised Fukuoka criteria were used. Disease progression was noted in 130 (24.1%) patients. The probability of progression was 3.7% during 1 year, 23.4% during 5 years, and 43.3% during 10 years. Surgical treatment was performed in 15 (2.8%) patients. In 7 (1.3%) patients, cancer was found, and 3 (0.56%) patients died of pancreatic-associated disease. Initial cyst size > 15 mm, body mass index > 26.4 and heavy smoking were independent progression risk factors. The authors analyzed the association between AB0 blood group and progression risk. The higher association of AA group compared to 00 group with progression was also associated. The authors concluded that IPMN diameter alone is not a sufficient for the assessment of progression risk; however, it is useful in correlation with correlated with other features in observation of BD-IPMN patients[46].

Kwon *et al*[47] validated the current guidelines on BD-IPMNs in a meta-analysis including 40 studies (6301 patients). In this meta-analysis, HGD or pancreatic cancer was significantly associated with clinical manifestation, cyst diameter ≥ 30 mm, thickening of the cystic wall, mural nodules, MPD dilatation, abrupt MPD diameter changes, lymphadenopathy, increased CA 19.9 and increased CEA[47].

Srinivasan *et al*[48] published a systematic review to assess the clinical utility of the Sendai Consensus Guidelines and Fukuoka Consensus Guidelines for IPMNs. This review included 10 studies assessing the Fukuoka guidelines, 8 assessing the Sendai criteria and 4 assessing both guidelines. Pooled analysis showed that 751 of 1801 (42%) Fukuoka-positive neoplasms were malignant, and 599 of 697 (86%) Fukuoka-negative neoplasms were benign. The PPVs of the high-risk and worrisome-risk groups were 465/986 (47%) and 239/520 (46%), respectively, while 265 of 802 (33%) Sendai-positive neoplasms were malignant and 238 of 266 Sendai-negative (90%) neoplasms were benign. In conclusion, a higher PPV was noted in the Fukuoka compared to the Sendai criteria. However, the NPV of the Fukuoka guidelines was slightly lower compared to the Sendai guidelines. A higher PPV and lower NPV was reported in the Fukuoka compared to the Sendai criteria. Thus, malignant and even invasive IPMNs may be missed using both guidelines[48].

The participants of the Verona Evidence-Based Meeting on IPMN[49] assessed and compared the dissemination, use in clinical practice, and reliability of current guidelines for the management of PCNs. PCN classification as well as clinical and radiologic features were based on the IAP, European guidelines, and AGA recommendations. The answers to 47 questions were collected from 259 international responders, including participants from Europe (86%), Asia (8%), and the United States (6%). Among the responders, 58% were surgeons and 38% were gastroenterologists. The European guidelines were the best-known (79%), followed by IAP (69%) and AGA (61%) recommendations. The diagnostic investigations (MRI, CT, EUS, and cyst fluid analysis) were known by all participants; however, contrast-enhanced EUS was available only for 41% of responders. The analysis showed that guidelines were the most widely disseminated among surgeons and gastroenterologists, but the clinical application was decreased by the limited availability of diagnostic examinations. For example, contrast-enhanced EUS examination is not available for > 50% of physicians. Although enhancing mural nodules ≥ 5 mm, considered high-risk stigmata, are absolute indications for surgery, according to >30% of physicians, this feature was not a sufficient indication for surgery. Therefore, according to Verona EBM experts, some questions (including the role of mural nodes in patients during follow-up, the correlation between imaging and histopathological findings, the optimal diameter

cutoff for the optimal assessment of the risk malignancy, and the most accurate imaging for optimal diagnosis) should be resolved. Despite of knowledge of the increased rate of malignant transformation in resected IPMNs with an MPD of diameter 5.0-9.9 mm, according to > 80% of responders, this feature was not a sufficient indication for surgery. Without prospective observational data on the observed IPMN, moderate MPD dilatation alone was not associated with an increased perception of cancer risk by clinicians. According to > 60% of responders, IPMN diameter and cyst growth rate were not enough indications for surgery. According to Verona EBM participants, further studies regarding IPMN-related symptoms as indications for surgery are needed. The guidelines should be more detailed to identify patients requiring surgery due to clinical presentation to avoid unnecessary surgery. The length of follow-up is also questionable. According to the AGA guidelines, surveillance should be discontinued after 5 years in patients with a stable pancreatic cystic neoplasm. Only 18% of responders would consider to discontinue observation after 5 years, but according to 54% of them, there is not enough evidence to recommend lifetime observation. Therefore, further studies assessing the most cost-effective surveillance protocols and identifying the most suitable population for surveillance discontinuation are required. In addition, further studies, including randomized controlled trials, should identify patients requiring adjuvant treatment after surgery for invasive IPMNs. The authors of Verona EBM pointed to three levels of discrepancies regarding recommendations in pancreatic cystic neoplasms: among the 3 existing guidelines themselves, between guidelines and available evidence, and between guidelines and clinical practice. The role of MPD dilatation, mural nodules, tumor diameter and growth rate, tumor-associated clinical signs, and discontinuation of observation are the most important issues. According to experts, the current guidelines should be updated and unified to facilitate their use in clinical practice. The goal of Verona EBM participants was to define future research directions to increase the level of available evidence[49].

Prognosis of IPMN patients following surgery

The overall 5-year survival is reported to be 36%-77%. It depends on tumor advancement and the presence of malignant transformation in the resected tumor. The best prognosis is in benign IPMNs. The 5-year survival following surgery for non-invasive IPMN is 77%-100%. In malignant IPMNs, the prognosis is poorer. The 5-year survival rate following surgery for IPMN with invasive cancer is 27%-60%[5].

CONCLUSION

Clinical decision making for patients with pancreatic IPMNs is still challenging. While the management of MD-IPMN does not raise doubts and all guidelines require resection due to the high risk of malignant transformation, the management of BD-IPMN is controversial. The most important is the correct selection of patients requiring surgery at the right time, without unnecessarily exposing patients who do not require surgical treatment to complications related to pancreatic resection. It is known that pancreatectomy performed even in the most experienced centers is associated with the risk of complications. The correct algorithm of observation of patients not qualified for resection is also important. This review of the literature showed that the current guidelines are indeed useful in managing patients with IPMNs but are not ideal. Further prospective multicenter studies are needed to optimally select surgical candidates so that only those patients who need surgery are operated on and that treatment is avoided for the remaining patients who can be safely monitored.

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