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REVIEW

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Modern aspects of the management of pancreatic intraductal papillary mucinous neoplasms: a narrative review

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Abstract

Intraductal papillary mucinous neoplasms (IPMNs) account for approximately 35% of all cystic tumors in the pancreas and represent the largest subgroup. They are characterized by mucin production and intraductal papillary epithelium growth. IPMNs range from benign to malignant lesions. Biomarkers combined with ^{18}F-Fluorodeoxyglucose–positron emission tomography (^{18}FDG–PET) is the best diagnostic tool. The risk of malignant transformation for main-duct IPMNs is between 34–68% and for low-risk branch-duct (BD)-IPMNs it is 1.1%. Monitoring is crucial for determining the optimal time of surgical excision. Novel artificial intelligence combining clinical, tumor biomarkers, imaging and molecular genomics plays a determinant role in the evaluation of such lesions. The first diagnostic tool is multidetector helical computed tomography (MDHCT) or up-to-date magnetic resonance imaging (MRI). MRI detects malignancy by enhancing mural nodules ≥3 mm. Novel endosonographic interventional techniques have been added to the diagnostic armamentarium. Pancreatoscopy is feasible and effective but challenging for evaluating the diagnosis, invasiveness, and extent of IPMNs. Its findings may change the surgical approach. Pancreatic juice and duodenal fluid have been used recently for molecular biological analysis. The genes most frequently altered include Kirsten rat sarcoma viral proto-oncogene (*KRAS*), tumor protein p53 (*TP53*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), SMAD family member 4 (*SMAD4*), and guanine nucleotide-binding protein, alpha stimulating (*GNAS*). Despite the advances in diagnostic modalities, assessment of this premalignant lesion of pancreatic cancer, with its poor prognosis, is a challenging task. Pancreatectomy is the indicated approach for malignant or high-risk IPMNs with potent malignancy. Conservative management or enucleation for preserving the pancreas of low-risk BD-IPMNs is recommended, but long-term follow-up for recurrence is necessary. The management of IPMNs must be individualized based on preoperative high-risk stigmata and worrisome features.

Keywords: pancreatic cystic neoplasms, IPMN, pancreatic cancer, pancreatic cysts, mucinous neoplasms.

Introduction

IPMNs represent approximately 1% of all pancreatic neoplasms and 25–35% of all pancreatic neoplastic cystic lesions and comprise the largest subgroup [1–3]. This entity was first described by Ohashi, in 1982, as a tumor distinct from mucinous cystic neoplasms (MCNs) and pancreatic ductal adenocarcinoma (PDAC) [3]. Their specific characteristics are the intraductal production of mucin and the growth of the papillary epithelium [2]. They cause recurrent episodes of acute pancreatitis and eventually lead to pancreatic dysfunction. However, IPMN may also be asymptomatic. Their biological behavior ranges from benign to malignant. These lesions may coexist in patients with other cancers, *i.e.*, urogenital cancer, colorectal cancer (CRC) or in the first-degree relatives of people with CRC [1]. The increased risk of CRC and advanced polyps in patients with IPMN mandates their relevant follow-up and management when such a diagnosis is made [4].

Despite advances in diagnosis and treatment, PDAC is one of the most lethal malignant diseases, with an overall 5-year survival not exceeding 10%. Among all gastrointestinal (GI) malignancies, it is the deadliest. Its incidence is increasing worldwide, and in most cases (80%), it is inoperable at the time of diagnosis. IPMNs are regarded as precursor lesions of invasive pancreatic carcinoma [5].

Hereditary pancreatic cancer accounts for approximately 10% of all pancreatic cancers. The early diagnosis of precancerous pancreatic cysts is currently attracting great interest in efforts to improve the outcomes of pancreatic cancer management. IPMNs, which have a high incidence among members of families with hereditary pancreatic cancer, are considered precancerous lesions. The detection of gene mutations is of great importance in identifying cases with an increased risk for carcinogenesis [6]. The oncological outcomes of high-risk patients who undergo surgery are comparable to those of the general population [7]. For high-risk cases, pancreatic cancer screening by three annual magnetic resonance imaging (MRI)–magnetic resonance cholangiopancreatographies (MRCPs), even in community-based efforts, has been recommended [8] since high-risk patients could benefit from such frequent surveillance [9].

There are three types of lesions with different biological behaviors, *i.e.*, main-duct (MD)-IPMNs, branch-duct (BD)-IPMNs or mixed IPMNs [2, 10].

As independent predictive factors for malignancy in MD-type IPMNs, the presence of symptoms, main pancreatic duct equal to or greater than 10 mm in diameter, thickened wall, mural nodule, and distal parenchymal atrophy have been identified. In the case of a main pancreatic duct 5–9 mm in diameter accompanied by the presence of at least one other predictive factor, the risk of malignancy is 35%, and immediate surgical intervention is necessary [11]. In MD-type IPMNs, two other independent determinants predicting high-grade dysplasia or invasive carcinoma were revealed by multivariate analysis. They include the height of the mural nodule (equal to or more than 5 mm) and the carcinoembryonic antigen (CEA) level (equal to or more than 50 ng/mL) in the pancreatic juice and indicate an immediate need for surgical intervention [12].

The natural progression of BD-IPMNs in patients with a genetic predisposition to pancreatic cancer [a germline mutation in breast cancer 1 (*BRCA1*) or breast cancer 2 (*BRCA2*) genes] has been recently evaluated [13]. Among the patients with these mutations, the predominance of BD-IPMN was 13.6% (mean cyst size 7.7 mm), and that of pancreatic cancer was 3.1%. Approximately similar results were obtained in a long-term follow-up (mean 5.3 years) to detect the development of new cases. Patients with alterations in the *BRCA2* gene compared to the *BRCA1* gene had an almost four times greater susceptibility to pancreatic cancer development, but there was no difference between these genes in the prevalence of BD-IPMN.

The detection of BD-IPMNs by modern imaging appears to have an increasing incidence. It is important to identify those at the lowest risk of progression to malignancy to avoid subjecting them to unnecessary surveillance or treatment [14]. There has been an evolution in diagnostic modalities, including imaging tools, laboratory tests, molecular markers, pancreatoscopy, pathology and artificial intelligence (AI). multidetector helical computed tomography (MDHCT) is the preferred method along with up-to-date MRI for the initial evaluation of patients in whom a pancreatic lesion is suspected. Endoscopic ultrasound (EUS) is the second diagnostic tool [11, 14]. IPMNs as all pancreatic cystic lesions can be incidental findings on computed tomography (CT) performed for other reasons unrelated to pancreas, such as CT colonography [15].

Surgery is the cornerstone of treatment. The median survival outcome after surgery is significantly worse in invasive IPMNs than in MCNs. Adjuvant chemotherapy in addition to surgical resection may further improve survival and is considered necessary in advanced cases [16].

The ABO blood group may influence the risk of malignancy development in IPMN. In resected IPMNs, the prevalence of IPMN was found higher in patients with non-O blood group than in the general population and these patients had a significantly higher likelihood of finding invasive carcinoma. [17].

Aim

In this narrative review, we highlight the current data on genomic profiling, diagnosis, and treatment of IPMNs, providing comprehensive, complete, and modern knowledge to manage them.

Genomic profiling – molecular alterations

The most common molecular alterations in pancreatic cancer involve mutations in the Kirsten rat sarcoma viral proto-oncogene (*KRAS*), tumor protein p53 (*TP53*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and SMAD family member 4 (*SMAD4*) genes. Pancreatic cancer related to IPMN, according to the international guidelines, may either be derived from IPMN transformation or be concomitant with IPMN in different locations in the pancreas. However, there have been no significant differences noted between pancreatic cancer alone and pancreatic cancer concomitant with IPMN in genetic alterations, the immune and fibrotic status of the tumor microenvironment and its prognosis. Additionally, the overall survival (OS) and disease-free survival (DFS) were not different between these groups of patients, and the coexistence of IPMNs does not worsen the prognosis of pancreatic cancer [18]. Determination of the molecular pathways involved in pancreatic cancer and IPMN is of great importance for an early diagnosis and further improvements of clinical outcomes [5].

Pancreatic cancer may be derived from several pre-malignant lesions, including intraductal tubulopapillary neoplasm (ITPN) [19]. Molecular analysis of precursors of pancreatic cancer with gastric and intestinal phenotypes, such as the trefoil factor 3 (*TFF3*) gene, mucin 2 (*MUC2*) gene and mucin like 3 (*MUCL3*) gene, showed their molecular heterogeneity, which is possibly related to their different cell identities and etiologies [20].

The molecular mechanisms involved in the IPMN development and its subsequent progression to pancreatic cancer are mostly unknown. The switch/sucrose non-fermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (*SMARCA4*) gene contributes to the formation of Brahma-related gene 1 (BRG1) protein and of SWI/SNF protein complexes. A possible mechanism has recently been reported. The loss of BRG1 protein cooperates with the *KRAS* gene to form IPMN and then it progresses to pancreatic cancer. A better understanding of these mechanisms may lead to new diagnostic and therapeutic guidelines [21].

There are three categories of molecular alterations in tumors of the pancreas: (*i*) constitutive activation of the *KRAS* gene, which normally exists in an inactive form, was found in over 90% of cases; (*ii*) the absence of functional suppressor genes, *i.e.*, *TP53*, *p16*, *CDKN2A* and *SMAD4*; this causes uncontrolled proliferation and dissemination of cancer cells by promoting apoptosis (programmed cell death); and (*iii*) inactivation of human MutL homolog 1 (*hMLH1*) and MutS homolog 2 (*MSH2*) genes that repair deoxyribonucleic acid (DNA) damage. Specifically, for IPMNs, the *KRAS* gene (90%) initiates its development, and the guanine nucleotide-binding protein, alpha stimulating (*GNAS*) gene (40–60%) may influence the characteristic phenotype of IPMN. In the vast majority (90%) of IPMNs, there are mutations in at least one of the *KRAS* genes or the *GNAS* gene, and in 40%, there are mutations in both genes. Other involved genes include ring finger protein 43 (*RNF43*) (25%), *TP53* (10%), *SMAD4* (rare) and *BRCA1*/*BRCA2* (14%) [3, 22]. Alterations of these genes have been

identified in pancreatic juice, blood, or surgical resection specimens [3].

Mutations in oncogenic *GNAS* drive the pancreatic tumorigenesis and are commonly found in IPMNs. This GNAS pathway induces mucin production not only *via* the *MUC2* gene but also *via* the mucin 5AC (*MUC5AC*)/ mucin 5B (*MUC5B*) gene. However, most importantly, the conflict of mutations in the *GNAS* gene with the KRAS signaling pathway can limit tumor aggressiveness by blocking the neurogenic locus notch homolog (NOTCH) signaling. Thus, it can moderate the aggressiveness of the tumor and ameliorate the outcomes [23].

Mutations in the *GNAS* gene are related to decreased perivascular invasion, perineural invasion and lymph node involvement and ultimately to increased OS. The coexistence of mutations in both *KRAS* and *GNAS* was mainly present in BD-IPMNs [24]. This may explain their more benign course.

IPMN organoids harboring *GNAS*, *RNF43* and KLF transcription factor 4 (*KLF4*) mutations have been grown. The motor neuron and pancreas homeobox 1 (MNX1)–hepatocyte nuclear factor-1-beta (HNF1B) axis is necessary for IPMN lineages [25].

A meta-analysis identified 270 upregulated and 161 downregulated genes that were characteristically altered in high-risk IPMNs. There were key changes in gene expression between low-risk and high-risk IPMNs. However, 12 genes were altered significantly, and the so-called "12-gene signature" has been proposed as a potential biomarker in the pancreatic juice for the identification of IPMNs that have a high risk for malignant development [26].

The key signaling pathways or protein complexes involved in the pathogenesis of IPMNs include G-protein-coupled receptor (GPCR), transforming growth factor (TGF), SWI/SNF, WNT and phosphatidylinositol 3-kinase (PI3K) [27].

A polymorphic variant in telomere maintenance is related to the appearance of worrisome features (WF) and high-risk stigmata (HRS). Telomere length measured in lymphocytes predicts the risk of IPMN progression to pancreatic carcinoma. It is genetically determined by single nucleotide polymorphisms (SNPs) using 11 variants alone or combined [acylphosphatase 2 (*ACYP2*)-*rs11125529*, PX serine/threonine kinase (*PXK*)-*rs6772228*, telomerase ribonucleic acid (RNA) component (*TERC*)-*rs10936599*, nuclear assembly factor 1 ribonucleoprotein (*NAF1*)-*rs7675998*, telomerase reverse transcriptase (*TERT*)-*rs2736100*, oligonucleotide/oligosaccharide-binding fold containing 1 (*OBFC1*)-*rs9420907*, CST telomere replication complex component 1 (*CTC1*)-*rs3027234*, zinc finger protein 208 (*ZNF208*)-*rs8105767*, zinc finger protein 676 (*ZNF676*)-*rs412658*, DEAH-box helicase 35 (*DHX35*)-*rs6028466*, zinc finger and BTB domain containing 46 (*ZBTB46*)-*rs755017*] that affect telomere length (teloscore). This teloscore showed no association with progression to pancreatic cancer, except the *PXK-rs6772228-A* variant that had an increased risk of such progression [28].

Diagnosis

The newest edition (the 5th in 2019) of the *World Health Organization* (WHO) Guidelines classified the intraductal precursors of adenocarcinoma as IPMNs and included the previously considered variants of IPMNs, *i.e.*, intraductal oncocytic papillary neoplasms (IOPNs) and ITPNs, as distinct neoplasms [10, 29]. The dysplasia of these lesions may be either of low grade or high grade, and they eventually progress to invasive carcinoma. IPMN have the potential to progress towards malignancy, but the majority will not progress to invasive carcinoma. The incidence of concomitant pancreatic cancer in patients with IPMNs has been reported to be between 2.5% and 9.2%. It is less aggressive with longer survival than that unrelated to IPMNs. However, the concomitant cancer incidence is higher in IOPNs (30%) and ITPNs (70%) [10].

Modern imaging techniques (EUS, contrast-enhanced US, MRCP, MDHCT) may differentiate IPMNs from other pancreatic cystic lesions and be used to assess the main pancreatic duct dilatation and its characteristics for potential malignancy [30–32].

The *Fukuoka International Consensus Modified Guidelines* (2017) recommended the "high-risk stigmata" and "worrisome features" as indications for the immediate surgical resection of IPMN. The HRS include a dilated main pancreatic duct (≥10 mm), obstructive jaundice and an enhanced solid component. The WF on imaging include a cyst size equal to or larger than 3 cm, thickened and enhanced cyst walls, abrupt dilatation of the main pancreatic duct (5–9 mm in diameter), distal atrophy of the pancreas, non-enhancing mural nodules and lymph node involvement [10, 33, 34]. The presence of HRS is associated with a strong possibility for malignant transformation. Likewise, a similar risk exists for ≥3 WF [35].

In a study including 131 patients who were operated on for IPMN, invasive carcinoma was finally confirmed in 22% of cases. Univariate analysis identified an enhancing mural nodule ≥5 mm, obstructive jaundice, abrupt pancreatic duct dilatation, distal pancreatic atrophy, and lymphadenopathy as significant predictive factors for invasive carcinoma. However, the multivariate analysis limited these independent factors to three, enhancing mural nodule ≥13 mm, obstructive jaundice, and an abrupt dilatation of the pancreatic duct [36].

Apart from cyst size (≥15 mm), body mass index (BMI) ≥26.4 kg/m^2 and heavy smoking were found to be independent risk factors for BD-IPMN [33].

Mural nodules, the main pancreatic duct more than 5 mm in diameter and elevated carbohydrate antigen 19-9, also called cancer antigen 19-9 (CA19-9), serum levels are related to malignancy [37].

Calcification in malignant IPMNs was significantly higher than that in benign IPMNs. This, together with age more than 55 years and atrophy of the pancreatic parenchyma, are considered independent predictive factors for malignancy in patients with a pancreatic mass [38].

It has been found that diabetes mellitus (DM) lasting less than four years (new in onset) in patients with pancreatic cystic neoplasm including IPMN was a risk factor for malignant progression, insulin resistance, weight loss, and *SMAD4* mutation. The latter might explain the link between new-onset DM and pancreatic cystic neoplasm malignancy. SMAD4 protein induces negative regulation of the TGF-β signal pathway. It promotes malignant transformation, invasion, and metastatic capacity [39].

MRI–MRCP and MDHCT of a dual-phase pancreatic protocol may precisely assess the cyst size, morphology, and the pancreatic ductal system and identify high-grade dysplasia and invasive carcinoma with a diagnostic accuracy of 75–86% [2, 10, 33, 40]. Multiphase CT radiomics could further improve the diagnosis of malignant IPMNs [41]. MRI is important for detecting malignancy of IPMNs by enhancing mural nodules equal to or greater than 5 mm [42] or detecting pancreatic atrophy [43]. They are the first-choice diagnostic imaging modalities for further evaluation of any suspected lesion of the pancreas followed by EUS. Novel diagnostic tools, including cyst fluid analysis, laser endomicroscopy and AI, can assist in the recognition of patients at the highest risk for malignancy [44].

EUS is the most accurate method for detecting mural nodules in the pancreatic parenchyma and cystic component [2, 45, 46]. For the former, contrast harmonic enhanced EUS is superior to conventional EUS and can assess the blood flow of mural nodules, discerning them from mucin plugs [44]. AI may be used as a unique tool to augment the performance of EUS and improve its diagnostic ability [47–49].

EUS-guided fine-needle aspiration (FNA) provides samples for cytological, biomarker or molecular examination [10, 44, 50–52]. The accuracy of pancreatic EUS-guided fine-needle biopsy (FNB) is high, up to 85% [53–55], as its molecular analysis [56].

The assessment of IPMN malignancy by positron emission tomography (PET) using ^{68}Gallium-labeled fibroblast activation protein inhibitor (^{68}Ga–FAPI)–PET may be a helpful new diagnostic modality [57]. Additionally, MRI assessment of cyst fluid together with other signs may predict the malignant transformation of IPMNs [58], assisted by three dimensional (3D)–MRCP [59] or 3T MRI [60]. It has been postulated that ^{18}F-Fluorodeoxyglucose (^{18}FDG)–PET is the best imaging tool for malignant cystic lesions [61]. A screening system using forward viewing radial EUS and MRI/MRCP for screening individuals with a family history of pancreatic cancer has been proposed [62].

On endoscopy, the papilla appearance, such as a wide open "fish mouth" extruding mucus, is the pathognomonic finding of MD-IPMNs. Endoscopic retrograde cholangio-pancreatography (ERCP) and pancreatoscopy can be used to collect pancreatic juice for assessment [10]. Pancreatoscopy provides direct vision of the pancreatic duct and samples for biopsy by microforceps, which improves the diagnosis [44, 63, 64].

Needle-based confocal laser endomicroscopy (nCLE) is an endoscopic modality that provides high-resolution images of the GI tract mucosa [33, 44].

A novel use of natural language processing software to reveal worrisome lesions of the pancreas for potent malignancy on CT performed for other unrelated reasons has been proposed [65]. Additionally, a model of the GaWRDenMap framework is based on the concepts of geographically weighted regression and a density function-based classification model. It was applied to multiplex immunofluorescence images of pancreatic diseases. This application can discriminate between pancreatic cancer and IPMN [66].

Biomarkers

CA19-9 is the most widely used serum biomarker for detecting pancreatic cancer with high diagnostic efficacy (sensitivity 72%, specificity 86%) that is not affected by DM. The most commonly used cutoff is 37 U/mL, and values above 100 U/mL indicate a very high risk [67]. However, it may be found moderately raised in benign conditions with inflammation. Therefore, the use of serum CA19-9 as a single diagnostic indicator or as a screening indicator in general populations is not recommended. It may be useful in combination with other diagnostic tools in discriminating benign IPMNs from those with malignancy [2].

A retrospective cohort study assessed five serum tumor markers (CA19-9, CEA, CA125, CA72-4, and CA242) for identifying advanced MCNs and distinguishing IPMNs and MCNs. CA19-9 has a moderate accuracy, while CEA, CA125, and CA72-4 have a low accuracy. Perhaps a combination of marker testing can improve the outcomes [68].

Among 249 full-length recombinant human protein microarrays, 14 autoreactive proteins (autoantibodies) were identified as potential biomarkers for low-grade or high-grade IPMNs [69].

Protein analysis of pancreatic juice or cystic fluid included CEA, monoclonal antibody (mAb) Das-1 and amylase. CEA is the most studied biomarker. The cutoff value is 192 ng/mL. Values above 200 ng/mL indicate a strong possibility for mucin-producing neoplastic lesions [10, 44]. mAb Das-1 is a monoclonal antibody that detects high-risk IPMNs, with a sensitivity of 89% and specificity of 100% [10]. High amylase levels indicate communication with the main pancreatic duct, suggesting a pseudocyst or IPMN [10]. In addition, several other cyst fluid protein analysis markers [soluble Fas ligand (sFasL), CA72-4, matrix metalloproteinase 9 (MMP9), and interleukin (IL)-4] have been proposed [70].

The apolipoprotein A2-isoforms (apoA2-i) blood test is a promising biomarker to identify individuals at high risk for pancreatic cancer that may be in a curative stage [71].

Some microRNAs (miR-31-5p, miR-483-5p, miR-99a-5p, and miR-375) have been correlated with the malignant progression of IPMNs and may contribute to the discrimination of malignant from benign neoplasms [72].

In IPMNs with high-grade dysplasia, a relative depletion of T-cells with enriched macrophages is present compared to low-grade dysplasia [73, 74].

Glycogen synthase kinase-3beta (GSK-3β) and KRAS^{G12D} promote the retention of pancreatic ductal progenitor cells and are new lineage biomarkers related to IPMN and pancreatic cancer [75].

In current clinical practice, none of the known biomarkers allow for the selection of candidates for surgery, observation, or neither [76]. The serum biomarker fucosylated α_1-acid glycoprotein (fAGP) indicates malignant potential and, in combination with ^{18}FDG–PET/CT, is a valuable diagnostic tool [77].

Pancreatic juice and duodenal fluid obtained by endoscopic methods have been used recently for molecular

biological analysis [78, 79]. A recent meta-analysis including 32 studies and 939 cases of DNA analysis, found that mutations in *KRAS*, *TP53*, *CDKN2A*, *GNAS* and *SMAD4* have a high specificity (approaching 100%) for high-grade dysplasia or pancreatic carcinoma [80]. However, a previous meta-analysis including 44 studies and 2088 IPMN patients, provided evidence that, although *KRAS* and *GNAS* mutations are helpful in the preoperative diagnosis of IPMN, are not specific for high-grade or invasive IPMN [81].

Circulating cytokines, including tumor necrosis factor-alpha (TNF-α), IL-2R, IL-6 and IL-8, may predict malignant IPMNs. A novel nomogram including these cytokines and two HRS features (the presence of an intraductal solid component and main pancreatic duct dilation ≥10 mm) has been developed [82].

In the case of IPMNs, pancreatic parenchyma is often accompanied by fatty infiltration. Decreasing CT pancreatic density (pancreatic index, PI) may be an optimal imaging biomarker for earlier detection of malignancy [83].

Inflammatory markers (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio [84], advanced lung cancer inflammation index) are associated with the invasiveness of IPMNs, and a new nomogram has been developed [85]. The platelet-to-lymphocyte ratio [84] and the C-reactive protein to albumin ratio may be predictive markers of IPMN malignant transformation [86]. Elevated serum ferritin levels are related to malignant IPMNs [87]. Additionally, immunohistochemical detection of the expression of insulin-like growth factor II messenger RNA (mRNA) binding protein 3 (IMP3) in pancreatic juice is promising [88].

The gut microbiome may play a role in pancreatic cancer initiation and progression, and thus, the role of the pancreatic microbiota in the cystic liquid can be assessed for the detection of IPMN malignancy [89].

In tissue sample biopsy, the growth of neural structures within tumors is now considered a vital factor for carcinogenesis [90].

Management

The balance between the risk of malignancy and any risks of resection controls the decision on the management policy [91–94]. However, it must be individualized, considering several preoperative factors [95–97]. Nomograms have been proposed for the estimation of operative risk during decision-making [98]. They are based on preoperative factors [indicator for surgery, *American Society of Anesthesiologists* (ASA) score, BMI, white blood cell (WBC) count, alkaline phosphatase]. In addition, early postoperative factors (intra-operative blood transfusion, operation time, maximum WBC count on days 1 to 3, maximum serum amylase on days 1 to 3) may help predict the outcome [98].

The vast majority of MD-IPMNs and mixed IPMNs are amenable to surgical intervention. Their low coincidence with invasive pancreatic cancer usually allows for a more conservative approach to BD-IPMNs. In any case, strict postoperative follow-up is recommended even with negative resection margins because of a high risk for recurrence and possible metachronous lesions [99]. Therefore, the management of MD-IPMNs has been adequately clarified, while that of BD-IPMNs is still under debate. For BD-IPMNs, the presence of WF is considered a low risk for malignancy, but the presence of HRS increasing the likelihood for malignancy indicates a need for immediate resection [100]. In MD-IPMNs, despite the agreement thus far for pancreatectomy, some recent data recommend imaging surveillance in cases with a main pancreatic duct diameter between 5 mm and 9 mm, without symptoms or HRS. It has been postulated that this mild dilation alone may lead to potent misdiagnosis and subsequent overtreatment [2].

A recent study including 214 cases of BD-IPMNs found a 54.2% rate of high-grade dysplasia or invasive pancreatic carcinoma, which occurred in parallel with an increased diameter of the pancreatic duct. It was 29.8% for 5–10 mm diameters, 59% for 10–14 mm diameters, 78.6% for 15–19 mm diameters and 95.8% for ≥20 mm diameters. Likewise, the extent of dilation was found to have a similar correlation to *in situ* or invasive carcinoma. Upon follow-up lasting, on average, 50 months after partial pancreatectomy, 7.2% of patients without initial malignancy developed *in situ* or invasive carcinoma in the pancreatic remnant. This was not associated with the abovementioned pancreatic duct characteristics but only with the presence of mural nodules on preoperative imaging [101].

Pancreatectomy with standard lymphadenectomy has been indicated in confirmed or suspected invasive cancer [2]. It can be safely performed even in selected older patients with low morbidity and mortality [102]. The type and extent of excision depend on the IPMN's location. Adequate surgical resection from an oncological point of view and annual follow-up should be ensured [30].

As already known for a long time, main pancreatic duct dilatation equal to or greater than 10 mm, an enhanced mural nodule equal to or greater than 5 mm, obstructive jaundice and a positive cytological test are risk factors for malignant IPMNs. Among them, the most important is the mural nodule, and surgical resection is indicated in its presence [103]. The location of the lesion determines the type of pancreatectomy (proximal pancreaticoduodenectomy, distal or total pancreatectomy) by an open or laparoscopic approach. However, intraoperative frozen sections are highly reliable for margin evaluation and should always be performed after proximal or distal pancreatectomy to ensure an appropriate resection extent [103, 104].

Episodes of recurrent acute pancreatitis may by themselves be an indication for pancreatectomy for IPMNs. The rate of malignancy is similar between those with acute pancreatitis and those without it [105].

High-risk patients with MD or mixed IPMNs unfit for surgery had a 36% greater risk of developing pancreatic malignancy within a median of 2.5 years [106].

Angiotensin-converting enzyme inhibitors might slow the progression of BD-IPMNs. The matter is subject to further prospective research studies [107].

The fact that IPMNs may be multifocal (two or more pancreatic lesions) creates management dilemmas. However, it has been found that no differences exist in survival and grade of dysplasia between patients with unifocal and

multifocal IPMNs. Likewise, neither cysts in the remnant pancreas nor total pancreatectomy influence survival [108]. Undoubtedly, the latter is better from an oncological point of view in malignant cases, but the related morbidity and altered quality of life do not justify its choice for IPMNs based only on high-risk factors and no proven malignancy.

In malignant cases, recurrence after pancreatectomy may be local in the remnant pancreas or in distant extra-pancreatic tissue. Repeat pancreatectomy is recommended for recurrence in the remnant pancreas. Because of it, optimal surveillance for recurrence is essential for the timing of the reoperation [109].

A recent multicenter retrospective study of 837 patients with BD-IPMN and long-term active surveillance found that nonoperative management is safe and effective in cases without WF or HRS. Only 1.1% revealed invasive cancer. Factors related to WF/HRS included localized IPMN, diameter of the main pancreatic duct between 3 mm and 5 mm and a cyst size equal to or greater than 20 mm. The interesting new finding of this study was the diameter of the pancreatic duct [110]. Current guidelines consider the presence of symptoms such as recurrent acute pancreatitis and the recent appearance of DM and/or obstructive jaundice, WF/HRS [10, 33].

Conservative management or enucleation (preferably laparoscopic) for preserving the pancreas in cases of low-risk BD-IPMNs is recommended, but long-term follow-up for recurrence is necessary [111–113]. In addition, the selection of cases for enucleation should be careful, and the operation must be performed by experienced surgeons. The complications and recurrence rates are similar to those after more extended excisions [113].

The role of adjuvant therapy for IPMN-associated pancreatic carcinoma remains unclear. Adjuvant chemotherapy did not improve survival. The survival was similar after pancreatectomy alone or with the addition of chemotherapy [114, 115]. Current data indicate that it may have a place only in advanced stage tumors equal to or beyond stage 2 and with affected lymph nodes [116].

EUS-guided fine-needle injection (FNI) is a minimally invasive emerging palliative therapeutic option for delivering specific chemotherapeutic or other antitumor agents in inoperable cases [44].

Given that the maintenance of enhanced immunity including cytotoxic and memory T-cells, and antigen-experienced T-cells and B-cells, has led to promising novel research findings. These open new horizons for the emerging use of immunotherapy (vaccines and other immunomodulatory factors) to interrupt the transformation of IPMNs to pancreatic carcinoma [117].

Prognosis

The overall 5-year survival has been reported to range from 36% to 77% [2].

The prevailing model of recurrence after intended curative resection for cancer derived from IPMN is systemic. This process starts before local recurrence. It has been postulated that grade 3 (poor differentiation) malignant lesions accompanied by nodal involvement will exhibit systemic recurrence, while when they have R1 resection (infiltrated excision margin), local recurrence will occur [118].

There have been different oncological outcomes reported regarding DFS and recurrence of invasive IPMNs (five years and 33%, respectively) and PDAC (two years and 68%, respectively)). Likewise, the most common site of IPMN recurrence was the lungs (38.5%), followed by the liver (28.6) and the locoregional region (15.4%), while for pancreatic cancer, it was the liver (45%), followed by the locoregional region (36.6%) and the lungs (13.1%). These better outcomes of invasive IPMNs were attributed to less neuroinvasion and nodal involvement compared to pancreatic cancer [119].

Invasive IPMNs have a less aggressive recurrence pattern than pancreatic cancer and reflect a more favorable OS [120].

A recent study found a 5-year survival rate of 34% after therapeutic excision of invasive IPMNs. Prognostic nomograms have been proposed based on seven factors, *i.e.*, age, marital status, histological grade, tumor (T) stage, lymph node (N) stage, metastasis (M) stage, and chemotherapy [121].

A lower incidence of advanced neoplasia has been found during extended surveillance among low-risk BD-IPMNs after five years of size stability [122].

Patients with IPMN-associated carcinoma who underwent proximal pancreatoduodenectomy (60%), distal pancreatectomy (20%), or total pancreatectomy (20%) had a median OS of 98.6 months if R0 resection was achieved (free resection margin ≥1 mm), 39.3 months with R1 resection (free resection margin <1 mm), and 22 months with R2 resection (direct margin involvement). Low-grade IPMN at the resection margin had no prognostic value [123].

A study involving 377 patients with BD-IPMNs who had a median follow-up of 5.4 years found that no patients with normal CA19-9 levels developed cancer or high-grade dysplasia. Additionally, those with stable, not growing cysts of less than 15 mm and without WF or HRS may not need to undergo imaging surveillance [124].

It is well known that in pancreatic cancer, the involvement of para-aortic lymph nodes is related to a dismal prognosis. However, in invasive IPMNs, a multivariable analysis found that positivity and lymph node ratio were not independent prognostic factors for death; the independent prognostic factors were age above 70 years and CA19-9 levels above >200 U/mL [125].

A study including 2264 cases with invasive IPMNs assessed the impacts of different metastatic patterns on the prognosis. Liver, lung, multiple other organ metastases and age above 60 years were found to be independent predictive factors of a poor prognosis. Isolated liver metastasis was associated with worse survival than lung or other organ metastases. As expected, patients with multiple metastases had the worst survival, while those without metastases had the best survival [126].

Another study found several independent predictive factors (age above 70 years, tumor location in the peripheral pancreas, high grade differentiation, surgery, chemotherapy and TNM stage) [127].

A multivariable analysis in a study including 424 patients with IPMN-associated pancreatic carcinoma found several independent predictive factors for shorter survival (age above 70 years, high CA19-9 levels, DM, IPMN-pancreatic cancer subtype, grade 3 tumors with advanced TNM stage) [114].

Conclusions

The modern management of pancreatic IPMNs has adequately clarified several aspects. The most common BD type is associated with a lower likelihood of malignancy than the MD or mixed type and requires a more conservative approach. Common molecular alterations in invasive IPMNs have been recognized, which opens up new diagnostic horizons. Novel CT and MRI techniques constitute the initial diagnostic step, followed by ERCP, EUS and perhaps pancreatoscopy. CEA, CA19-9, and some new biomarkers may contribute to identifying the risk of malignancy. FNB may confirm the preoperative diagnosis. There are WF, and HRS determine the therapeutic approach by providing an assessment of the risk of malignancy. Pancreatectomy is the cornerstone of treatment for malignant lesions or lesions at high risk for potential malignancy. However, the therapeutic strategy must be individualized to avoid overtreatment. In low-risk BD-IPMNs, conservative management or enucleation of the lesion is recommended. In any case, long-term follow-up is necessary because of the possibility of recurrence.

Conflict of interests

There is no conflict of interests associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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