Thirty Years of Experience with Intraductal Papillary Mucinous Neoplasm of the Pancreas: From Discovery to International Consensus

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Key Words

Branch duct type · EUS · IPMN · Main duct type · Pancreatic cancer

Abstract

Background: Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is characterized by intraductal papillary proliferation of mucin-producing epithelial cells that exhibit various degrees of dysplasia. IPMN is classified as the main duct type (MD-IPMN) and the branch duct type (BD-IPMN) according to the location of involvement, and into four histological subtypes (gastric, intestinal, pancreatobiliary, and oncocytic) according to the histomorphological and immunohistochemical characteristics. Mucin core protein expression correlates with the biological behavior and prognosis of the tumor. DNA analysis has shown that IPMN is associated with a number of gene mutations, but the roles of many of these mutations require further investigation. Most patients with MD-IPMN undergo tumor resection. Patients with BD-IPMN who do not undergo resection may develop malignant change, and concomitant separate pancreatic cancer occurs in 2–10% of patients with IPMN. Patients with a strong family history may develop multiple BD-IPMNs as well as concomitant pancreatic cancer. Malignant changes are relatively easy to detect, especially by endoscopic ultrasonography (EUS), but the optimal surveillance protocol is currently unclear. **Key Messages:** The 2012 guidelines for the management of IPMN recommend that patients with

‘high-risk stigmata’ (obstructive jaundice, enhanced solid component, and main pancreatic duct size ≥ 10 mm) should undergo resection. Patients with ‘worrisome features’ (cyst size ≥ 3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, main pancreatic duct size 5–9 mm, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy, lymphadenopathy, and clinical acute pancreatitis) should be evaluated by EUS. EUS is a more sensitive test than computed tomography or magnetic resonance imaging for the early detection of malignancy. **Conclusions:** Most patients with MD-IPMN should undergo tumor resection. Patients with BD-IPMN who do not undergo resection should undergo careful surveillance including EUS for the early detection of malignant change and separate pancreatic cancer.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas was first reported by Ohhashi et al. [1] in 1980. One of their patients had invasive IPMN with profuse mucin secretion, which formed a fistula draining into the common bile duct. The same authors reported four patients with main duct type IPMN (MD-IPMN) that was successfully resected, resulting in a better prognosis than in ordinary type pancreatic ductal adenocarcinoma [2]. A large number of similar cases have subsequently been re-

ported, and the definitions and nomenclature used to describe this tumor have been refined over time.

After a consensus meeting regarding the clinical management of IPMN at the biennial meeting of the International Association of Pancreatology (IAP) in Sendai, Japan in 2004, world experts issued international consensus guidelines for the management of IPMN and mucinous cystic neoplasm (MCN) of the pancreas in 2006 [3]. These guidelines greatly contributed to increased awareness and better understanding of these tumors, and facilitated further publication of numerous reports, especially regarding the clinical, radiological, histological, and genetic aspects of IPMN. The guidelines were revised in 2012 after the second consensus symposium during the IAP meeting in Fukuoka in 2010 [4]. This article reviews the evolution of the definitions and management of IPMN of the pancreas over the past 30 years. Readers may refer to a recent publication for more details [5].

Definitions and Classification

IPMN is characterized by intraductal papillary proliferation of mucin-producing epithelial cells. This tumor usually secretes excessive amounts of mucin, and was initially referred to as ‘mucin-producing pancreatic tumor’ in Japan. The epithelial cells exhibit a wide spectrum of dysplasia, from mild-, intermediate- and high-grade dysplasia to invasive carcinoma. The degree of epithelial dysplasia was formerly classified as adenoma, borderline tumor, or carcinoma; but the nomenclature was changed by the Fukuoka consensus guidelines, in accordance with the World Health Organization (WHO) classification [4, 6]. The former adenoma is now named mild or low-grade dysplasia, borderline tumor is now named moderate or intermediate-grade dysplasia, and carcinoma in situ is now severe or high-grade dysplasia [7]. At present, only invasive carcinoma derived from IPMN is considered malignant, and high-grade dysplasia is not considered malignant [4, 6]. However, this has recently been questioned, as there have been some reported cases of high-grade dysplasia recurring as a distant metastasis after resection [8, 9]. High-grade dysplasia is regarded as an indication for surgical resection as stated in the Fukuoka guidelines [4], although it is not clearly defined as malignant [6].

Profuse secretion of mucin by IPMN results in cystic dilatation of the pancreatic ducts (fig. 1). IPMN and similar lesions were previously referred to by a variety of names such as cystic adenocarcinoma [10], mucin-pro-

Fig. 1. Magnetic resonance cholangiopancreatography showing branch duct IPMNs. The largest lesion (arrow) is in the tail of the pancreas and the smaller lesions (arrowheads) are in the body of the pancreas.

ducing tumor [2], diffuse intraductal papillary adenocarcinoma [11], diffuse villous adenoma [12, 13], mucinous pancreatic duct ectasia [14], intraductal cystadenocarcinoma [15], intraductal mucin-hypersecreting neoplasm [16], mucinous ductal ectasia [17], papillary adenoma [18], intraductal mucin-producing tumor [19, 20], ductectatic type pancreatic ductal carcinoma [21], mucin-hypersecreting tumor [22], mucous-hypersecreting tumor [23], and intraductal papillary neoplasm [24]. Mucin-hypersecreting tumor was previously divided into the main duct type, the branch duct type, and the peripheral type according to the main location of the involvement. Mucinous cystic neoplasm (MCN) corresponds to the peripheral type, and IPMN corresponds to the main duct type and the branch duct type. The confusing terminology has now been improved by excluding the peripheral type from the classification of IPMN and clearly defining MCN as a separate entity.

The WHO [25] and Armed Forces Institute of Pathology [26] classifications clearly define IPMN and MCN as different entities. MCN is characterized by mucin-producing columnar epithelium supported by ovarian type stroma, and almost exclusively occurs in the body and tail of the pancreas in middle-aged women. In contrast, IPMN frequently occurs in the head of the pancreas in elderly men, and does not include ovarian type stroma. Histopathological examination is essential for differentiating between these two entities, but the clinical management is similar in many aspects [27].

Table 1. Consensus nomenclature and criteria for the classification of features of four histological subtypes of intraductal papillary-mucinous neoplasm of the pancreas (cited from reference 30 with permission)

Type	Mimicker	Criteria	Atypia	MUC1	MUC2	MUC5AC
Gastric	Gastric foveolae	Thick finger-like papillae, eosinophilic > basophilic cytoplasm, basally located nuclei. This type may have abundant flat areas	Mild/low-grade	–	–	+
Intestinal	Intestinal villous neoplasm	Villous papillae, basophilic > eosinophilic cytoplasm, enlarged oval and hyperchromatic nuclei with pseudostratification. This type may show low papillae consisting of cells with amphophilic cytoplasm	Moderate or severe/ high-grade	–	+	+
Pancreatobiliary	Cholangio-papillary neoplasm	Thin branching complex papillae, moderate amphophilic cytoplasm, enlarged hyperchromatic nuclei	Severe/high-grade	+	–	+
Oncocytic	Oncocytic neoplasm	Thick branching complex papillae with intracellular and intraepithelial lumina, abundant eosinophilic (oncocytic) cytoplasm, large round nuclei with prominent nucleoli	Severe/high-grade	+	–	+

In 1993, Osako et al. [28] reported that the mucin core protein expression of IPMN correlated with the biological behavior and prognosis of the tumor, and that MUC2 expression was associated with poorer clinical outcomes [29]. In 2005, Furukawa et al. [30] proposed the classification of IPMN into four histological subtypes (gastric, intestinal, pancreatobiliary, and oncocytic) based on the histomorphological features of papillary proliferation and the immunohistochemical characteristics of mucin glycoproteins (table 1). Gastric type IPMN has finger-like papillary growths that are positive for MUC5AC but not for MUC1 or MUC2, intestinal type IPMN has villous papillae that characteristically express MUC2 and MUC5AC but not MUC1, pancreatobiliary type IPMN has an intricate thin arborizing papillary structure that is consistently positive for MUC5AC and focally positive for MUC1 but not MUC2, and oncocytic type IPMN has complicated thick papillae consisting of eosinophilic oncocytic cells that are consistently positive for MUC5AC and focally positive for MUC1 and/or MUC2.

During the last decade, the histological subtype has been demonstrated to have clinical significance in terms of predicting the biological behavior and prognosis of IPMN [31–34]. Invasive carcinoma derived from the non-intestinal type IPMN is associated with a poor prognosis, characterized by lymphatic invasion and a tubular invasive pattern [31], whereas invasive carcinoma derived from intestinal type IPMN is of the colloid type and

is often minimally invasive [33]. It has been reported that the tumor stage is the most significant predictor of survival, followed by the histological subtype, which was a significant predictor in a subcohort of patients with invasive IPMN [32, 34].

Clinical Management

The treatment of MD-IPMN has not changed much over the past three decades. Most patients with MD-IPMN who are fit for surgery undergo tumor resection. However, the surgical indications for branch duct type IPMN (BD-IPMN) have become considerably more conservative over time.

The Sendai guidelines published in 2006 proposed a variety of strategies for the management of IPMN [3]. The guidelines recommended resection of most BD-IPMN measuring >3 cm in diameter even without mural nodules, and many patients with these tumors therefore underwent resection. As malignancy was found in 25.5% of all BD-IPMNs resected and invasive cancer was found in 17.7%, the Fukuoka guidelines included more conservative criteria for the surgical resection of BD-IPMN [4].

One of the remarkable characteristics of the Fukuoka guidelines was the adoption of two layers of criteria for assessment of IPMN: ‘high-risk stigmata’ considered to be indicative of malignancy, and ‘worrisome features’ possi-

bly pointing toward malignancy. The high-risk stigmata include obstructive jaundice, enhanced solid component, and main pancreatic duct size ≥ 10 mm, and patients with these features should undergo resection without delay. The worrisome features include a cyst size of ≥ 3 cm, thickened and enhanced cyst walls, nonenhanced mural nodules, main pancreatic duct size 5–9 mm, an abrupt change in the main pancreatic duct caliber with distal pancreatic atrophy, and lymphadenopathy on imaging examinations; and clinical acute pancreatitis. Patients with these features should be evaluated by endoscopic ultrasonography (EUS) for further risk stratification. Use of these two layers of criteria seems to result in more accurate assessment of the need for surgical treatment of BD-IPMN. EUS can demonstrate morphological features suggestive of malignancy such as mural nodules, irregularity and/or thickening of septa between cysts, and the presence of vascularity in these structures, and has gained an increasing role in the diagnosis of IPMN over the past decade [35]. Future surveillance of BD-IPMN will become increasingly reliant on the ability of EUS to detect malignant changes in IPMN.

Molecular and Genetic Investigations

In addition to the immunohistochemical mucin staining discussed earlier, genetic analysis of IPMN has progressed over recent years. DNA analysis by flow cytometry showed that IPMN tumor cells of intermediate-grade dysplasia were diploid, whereas those of high-grade dysplasia were aneuploid [36]. Two of five malignant MCNs were reported to be p53 positive, but there was no DNA aneuploidy in any of the 10 patients with IPMN (4 with low-grade dysplasia, 1 with intermediate-grade dysplasia, and 5 with high-grade dysplasia) [37].

The incidence of point mutations at codon 12 of the *KRAS* gene in IPMN has been studied [7, 38–43] extensively. Although *KRAS* point mutations are found in areas of low-grade as well as high-grade dysplasia, the frequency of the mutation generally increases with an increased degree of dysplasia. *KRAS* mutations were detected in the pancreatic juice of patients with IPMN, but also in the pancreatic juice of patients with chronic pancreatitis, and this is not a useful method of differentiating between carcinoma and adenoma [42]. A more recent study identified activating *GNAS* mutations at codon 201 as a highly specific genetic alteration in IPMNs [44, 45]. *BRAF* mutations also contribute to the oncogenesis of IPMN/IPM carcinoma (IPMC), but at a lower frequency than *KRAS* mutations [46]. More recently, whole-

exome sequencing revealed somatic mutations in *KCNF1*, *DYNC1H1*, *PGCP*, *STAB1*, *PTPRM*, *PRPF8*, *RNASE3*, *SPHKAP*, *MLXIPL*, *VPS13C*, *PRCC*, *GNAS*, *KRAS*, *RBM10*, *RNF43*, *DOCK2*, and *CENPF* genes in IPMN (table 2) [47, 48]. The same study found that 48 (40.7%) of 118 IPMNs, but none of 32 pancreatic ductal adenocarcinomas, harbored *GNAS* mutations. G-protein α -subunit is encoded by *GNAS* and its downstream targets, phosphorylated substrates of protein kinase A, and its expression in IPMN was found to be associated with the histological grade of IPMN. *GNAS* mutations are unique to IPMN, and activation of G-protein signaling may play a crucial role in IPMN progression. Amato et al. [49] reported an even higher frequency of *GNAS* mutation in IPMN (38/48; 79%) using next-generation sequencing. The second most common mutation was *KRAS*, found in 50% of IPMN, and the third most common was *RNF43*, found in 14%. *GNAS* and/or *KRAS* mutations were found in 92% of IPMNs. *TP53* and *BRAF* mutations were observed only in high-grade IPMN (10 and 6%, respectively).

In the latter half of the last three decades, investigation had focused on the molecular and genetic analysis of IPMN. The significance of *GNAS* mutations is relatively well understood, but the roles of other genetic mutations require further investigation.

Invasive Pancreatic Cancer Concomitant with IPMN

In the past two decades, the occurrence of coexistent but separate pancreatic cancer in patients with IPMN has been of particular interest. Tanaka et al. [50] first reported noninvasive pancreatic cancer concomitant with BD-IPMN in 1997. It has been proposed that the presence of BD-IPMN may be an indicator of noninvasive pancreatic cancer [51]. The same authors reported 76 patients who underwent resection of BD-IPMN, of which 7 (9.2%) had concomitant noninvasive or invasive pancreatic cancer [52]. Subsequent reports of cases [53, 54] and many series from Japan [55–62] indicate that concomitant pancreatic cancer occurs in 2–10% of patients with IPMN [63]. Even a small (≤ 1 cm diameter) BD-IPMN is associated with an 8% risk of developing distinct pancreatic cancer during surveillance [56]. The reported yearly incidence of distinct pancreatic cancer in patients with BD-IPMN is 0.41–1.10% [56, 58, 62].

Although the malignant changes of BD-IPMN are relatively easy to detect, especially by EUS [35], and the surgical indications for BD-IPMN even with mural nodules

Table 2. Mutations identified in IPMN by whole-exome sequencing (cited with modification from reference 47 with permission)

Gene	Accession No.	Mutation	Protein	Function*
GNAS	NM_000516	c.602G.A	p.R201H	G-protein beta/gamma-subunit complex binding
KRAS	NM_033360	c.35G.A	p.G12D	GDP binding
RNF43	NM_017763	c.931-932insC	p.L311PfsX132	Ubiquitin ligase activity
KCNF1	NM_002236	c.802G.A	p.V268M	potassium channel activity
DYNC1H1	NM_001376	c.9739C.T	p.Q3247X	ATP binding
PGCP	NM_016134	c.1388C.T	p.A463V	metal ion binding
STAB1	NM_015136	c.1504G.A	p.A514T	receptor activity
PTPRM	NM_001105244	c.1312G.A	p.E438K	protein tyrosine phosphatase activity
PRPF8	NM_006445	c.5525C.T	p.A1842V	RNA binding
RNASE3	NM_002935	c.164G.A	p.R55Q	ribonuclease activity
SPHKAP	NM_001142644	c.3710C.T	p.S1237L	protein binding
MLXIPL	NM_032954	c.2056C.T	p.R686C	transcription activator activity
VPS13C	NM_017684	c.5992A.G	p.I1998V	protein localization
PRCC	NM_005973	c.958C.T	p.P320S	protein binding
RBM10	NM_005676	c.1817-1818insA	p.E606EfsX37	RNA binding
DOCK2	NM_004946	c.3695-3700delTGGACT	p.L1232-C1234delinsR	GTP binding
CENPF	NM_016343	c.327-328insA	p.Q110TfsX10	chromatin binding

* Gene Ontology (<http://www.ebi.ac.uk/GOA/>).

G-protein = The guanine nucleotide-binding protein; IPMN = intraductal papillary mucinous neoplasm.

is becoming more conservative [64], effective surveillance strategies for the timely detection of concomitant pancreatic cancer in patients with IPMN are urgently needed. It is currently debated whether the imaging surveillance interval proposed for patients with IPMN by the Fukuoka guidelines is adequate, because even 6-monthly surveillance may miss the diagnosis of pancreatic cancer at a sufficiently early stage [65]. Kamata et al. [66] surveyed 102 patients with apparently benign BD-IPMN by 6-monthly EUS and other imaging examinations. They found distinct pancreatic cancer in 7 patients (7%), but no cases of malignant transformation of BD-IPMN. Interestingly, a combination of computed tomography and magnetic resonance imaging performed immediately after the detection of pancreatic cancer by EUS showed the lesion in only 43% of cases, indicating the pivotal role of EUS in the early detection of pancreatic cancer.

Some studies have investigated the characteristics of IPMN associated with distinct pancreatic cancer. Ideno

et al. [67] investigated the histological subtype of IPMN in patients with concomitant pancreatic cancer, and found a high frequency of gastric subtype. Concomitant pancreatic cancer may occur in patients with MD-IPMN as well as BD-IPMN [8]. Furthermore, distinct pancreatic cancer may develop even after the resection of IPMN. Ohtsuka et al. [68] reported that 17 (9.9%) of 172 patients who underwent resection of IPMN subsequently developed distinct pancreatic cancer. Noninvasive concomitant cancer can be detected early in patients with IPMN by cytological examination of pancreatic juice collected during ERCP or pancreatic resection [69, 70].

Familial pancreatic cancer has been extensively studied in select institutions, to explore the genetic, environmental, and lifestyle factors associated with its pathogenesis [71]. Patients with a strong family history of pancreatic cancer may develop multiple BD-IPMNs as well as pancreatic cancer during surveillance, and the presence of BD-IPMN may be a sign of concomitant high-grade

dysplasia, which was previously named pancreatic carcinoma in situ [72–74]. The Fukuoka guidelines recommend that the threshold for total pancreatectomy should be lowered in such patients, but there are currently insufficient data available to support this strategy.

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