Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Abstract

The introduction of the exocrine pancreatic classification by the World Health Organization and improvements in pancreatic imaging have led to an improved understanding of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. As a result, IPMNs of the pancreas are increasingly being recognized as a separate disease entity. IPMNs are characterized by the cystic dilatation of the pancreatic duct and its branches, with papillary projections. There are three histological subtypes of IPMNs: main duct, branch duct, and mixed. The degree of atypia ranges from adenoma to frank invasive carcinoma. The lymph nodes are involved considerably less frequently than they are in pancreatic adenocarcinoma. Most patients are symptomatic at diagnosis and require a diagnostic workup similar to that for patients with pancreatic adenocarcinoma. Although some investigators continue to advocate total pancreatectomy, the evidence in support of this is decreasing. Partial pancreatectomy remains the treatment option. Intraoperative assessment of the resection surgical margins is an important component of surgical resection. Additionally, controversy also exists regarding the nature of the follow-up

and the need for adjuvant chemoradiation therapy in the patient. Unlike ductal adenocarcinomas, IPMNs follow a relatively indolent course; the 5-year survival rate in patients with invasive IPMNs is 57%. A mural nodule and a main pancreatic duct diameter greater than 5 mm have been found to be predictors of malignancy.

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Introduction

Owing to the most recent World Health Organization (WHO) classification [1] and progress in investigational techniques, there is a plethora of publications on multiple facets of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. This increased understanding of IPMNs of the pancreas has led to the recognition that this tumor is distinct from other cystic tumors of the pancreas. IPMNs are characterized by cystic dilatation of the pancreatic ducts, with papillary projections in the presence of excessive mucin production. These tumors account for less than 10% of all pancreatic neoplasms. Like other pancreatic tumors, surgical extirpation is the primary method of treatment. There is, however, debate regarding the extent of the pancreatic resection. Unlike pancreatic adenocarcinomas, IPMNs follow a relatively indolent course; the 5-year survival rate for patients with invasive IPMNs is up to 60% [2].

Historical Background

IPMNs of the pancreas are described extensively in the Japanese literature. Ohashi et al. [3] first described IPMNs of the pancreas in 1981 in a report of 4 cases of mucin-producing cancers of the pancreas. IPMNs are also termed mucin-secreting carcinoma, villous adenoma of Wirsung's duct, diffuse intraductal papillary adenocarcinoma, intraductal cystadenoma, mucinous duct ectasia, and intraductal papillary mucinous tumors.

Increased recognition of IPMNs in the literature is explained by (a) the reclassification of exocrine tumors of the pancreas by WHO, (b) improvements in current pancreatic imaging techniques and therefore an improved understanding of IPMNs, and (c) better outcomes from pancreatectomy reported at high-volume centers. This latter has led to a higher rate of pancreatectomies.

Demographics

Patients with IPMNs of the pancreas present in the 6th to 7th decade of life and those with malignant IPMNs tend to be 6.4 years older than patients with adenomas or borderline lesions [2]. Despite the significant male predominance noted in early publications, current reports have described equal gender distribution [2, 4–7]. However, a recent publication of a large retrospective study from Asia showed a continued male predominance in this population, which raises the question of whether or not a geographic variation exists for IPMNs [8]. Interestingly, the median age of patients with IPMNs is two decades older than that of patients with chronic pancreatitis. IPMNs appear to demonstrate no racial predilection, as shown by several studies done in patients of different ethnic backgrounds [2, 4–9].

Histopathological Features of IPMNs

IPMNs encompass a wide spectrum of epithelial changes, ranging from adenoma to invasive adenocarcinoma, with borderline tumors and carcinoma in situ falling in between these two extremes [10]. As in patients with mucinous cystic neoplasms, the resected tumor must be extensively sampled by the pathologist to rule out cancer [11, 12].

There are three macroscopic subtypes of IPMN: main duct, branch duct, and mixed variant. In the Johns Hopkins Hospital experience [6], the branch-duct type was

the most common (46% of cases). Noninvasive IPMNs were in about 70% of branch-duct type. The main-duct type was the second most common type, accounting for about 28% of cases. Fifty percent of main-duct type tumors were noninvasive. The mixed-variant type was the least common type: (26%); 60% of these cases were noninvasive. The distribution of invasive IPMNs among the three subtypes was as follows: branch duct 30%, main duct 25%, and mixed variant 25%. On the other hand, in the series of Jang et al. [8], of 208 patients, more than 50% showed the macroscopic appearance of main-duct type. Likewise, D'Angelica et al. [5] noted that 69% of patients with IPMNs had the main-duct type.

The WHO classification of IPMNs categorizes these further into three histological types: adenoma, borderline (including in situ) cancer, and invasive cancer. Sohn et al. [6] found that borderline IPMNs are more common (62%) than the invasive type (38%). However, D'Angelica et al. [5] noted that the incidence of the borderline and invasive IPMNs is 15 and 48%, respectively. IPMN adenoma seems to be the least common histological subtype (10%) in most series [6].

It is important to distinguish IPMNs from other mucinous cystic neoplasms. Unlike IPMNs, mucinous cystic neoplasms are characterized by 'ovarian-like stroma' in histologic appearance, female gender predilection and distal location in the pancreas. Unless a fistula has formed to the pancreatic duct, mucinous cystic neoplasms rarely communicate with the pancreatic duct, whereas IPMNs commonly communicate with the pancreatic duct.

Molecular Features of IPMNs

K-ras Mutations and p53 Overexpression

The K-ras mutation is seen in 70–100% of patients with pancreatic cancer, and the prevalence of the mutation correlates with the degree of dysplasia. For example, the K-ras mutation is found in 16.7% of normal epithelium samples of IPMN but in 57.1% of specimens of high-grade dysplasia, carcinoma in situ and malignant forms of IPMN are combined; p53 overexpression has shown the same pattern, with more invasive types of IPMNs showing a greater overexpression of p53 [13].

Mucin Expression

Mucins (MUC 1–7) are glycoproteins expressed in different types of pancreatic neoplasms. MUC 2 and MUC 5 are highly expressed proteins in invasive-type IPMNs. However, MUC 1 is expressed in ductal adenocarcinoma

of the pancreas, but not in invasive IPMNs. Invasive IPMN patients with MUC5AC mRNA expression display better survival than those without MUC5AC mRNA expression [14].

DPC4 Gene

The DPC4 (deleted in pancreatic cancer 4) gene encodes a tumor suppressor protein that is relatively specific to pancreatic cancer and that is mutated in 45–55% of pancreatic adenocarcinomas. This mutation, resulting in the DPC4 inactivation, occurs due to one of two defects: a loss of heterozygosity (25%) or homozygous deletion (35%). On the other hand, in pancreatic adenocarcinomas, DPC4 is strongly expressed in all benign forms of IPMNs and in 84% of invasive IPMNs [7, 13, 15].

Predictors of Malignancy

Several studies have retrospectively analyzed clinical and pathological markers as predictors of malignancy [4, 5, 8]. Wiesenauer et al. [16] reviewed 64 consecutive cases with a pathological diagnosis of IPMN by analyzing 12 clinical symptoms and found that the onset of diabetes mellitus and jaundice were strongly associated with malignant IPMN. The study also showed that elevated serum alkaline phosphatase and glucose levels (as occur in diabetes) were strongly associated with invasive IPMN. Diabetes and jaundice were also found to be statistically significant, present in 140 patients with these tumors. Moreover, invasive adenocarcinoma was found in 60% of patients with main-duct IPMNs. Several Japanese authors also searched for predictors of malignancy but made different findings. For example, in a series of 62 patients with IPMN, Sugiyama et al. [4] identified two independent predictors of carcinoma: mural nodules and a main pancreatic duct diameter of 7 mm or more. Similarly, Jang et al. [8] noted in their series of 208 patients that mural nodule ($p = 0.009$), tumor diameter ≥ 3 cm ($p = 0.023$), and dilated duct size ≥ 12 mm ($p = 0.01$) were predictors of malignancy. Although some predictors of malignancy have been reported consistently, the relatively small numbers of patients involved preclude analysis of their sensitivity and specificity. Hence, these proffer minimal indication in clinical decision-making.

There is a lack of consensus regarding pretreatment predictors for differentiating various types of malignant IPMNs. The ability to stratify patients into low- and high-risk categories would allow more objective, evidenced-based recommendations on resection treatment. More-

over, in cases of partial pancreatic resections (pancreaticoduodenectomy or left pancreatectomy), an evaluation of other clinical, histological, and pathological markers would be helpful for follow-up and monitoring. Future research should focus on identifying clinicopathologic, radiologic and molecular factors that could be used for pretreatment risk assessment.

Clinical Presentation

Most reports suggest that more than 50% of patients with IPMNs are symptomatic [2, 5, 6], however, two thirds of the patients were asymptomatic at presentation in one study [17, 18]. A minority of published studies suggest that a sizeable proportion of IPMN patients is asymptomatic at diagnosis, due, in part, to the recent improvement in radiological imaging of the pancreas [6, 8, 19]. This fact, combined with the relatively indolent nature of some forms of the disease, creates challenges in individual patient management.

Unlike pancreatic ductal adenocarcinomas, 50% of patients with IPMNs of the pancreas present with abdominal pain, and up to 20% of patients with IPMNs present with acute pancreatitis, which, not surprisingly, has led to the diagnosis of chronic pancreatitis [2, 4, 6].

In patients with the invasive type of IPMN, weight loss and obstructive jaundice are the presenting features in 44 and 33% of the time, respectively [6]. However, patients with malignant IPMNs show a higher incidence of jaundice, recent onset or worsening of diabetes, longer duration of symptoms, and worsening abdominal pain compared to patients with benign IPMNs [2, 16]. There might also be accompanying weight loss: 20–40%; nausea and vomiting: 11–21%; back pain: 10%; steatorrhea: 6.5%; gastrointestinal bleeding: 2–4% and fevers: 2–4% [2, 5, 6, 16]. Although symptoms of jaundice or glucose intolerance might be more common, in patients with invasive forms of IPMN, the absence of these and other symptoms cannot be used reliably to exclude invasive IPMN.

IPMNs are distributed in the pancreas in the following proportions: head (50%), tail (7%), uncinate process (4%), and neck of the gland (4%). They may also occur throughout the gland in approximately 35% of cases [2].

Fig. 1. 46-year-old man with invasive IPMN identified on final histopathology. Contrast-enhanced preoperative baseline Multidetector CT image shows multiple cysts in the pancreatic head (white arrows) and soft tissue infiltrating into the pancreaticoduodenal groove (white arrowhead).

Diagnostic Workup

The diagnostic workup in patients with IPMNs of the pancreas is similar to that in patients with common pancreatic neoplasms. Following a thorough history and a physical examination, a complete blood count, electrolyte measurements, and a liver panel are performed. Since a proportion of patients present with a pancreatic mass, tumor markers, including CA 19-9, carcinoembryonic antigen, and CA 125 are also evaluated.

The primary imaging modality used to detect and evaluate IPMNs at the University of Texas M. D. Anderson Cancer Center is a thin-cut (2.5-mm sections, reconstructed to 1.25-mm sections) dual-phase pancreatic protocol Multidetector CT scan of the abdomen and pelvis. In addition to delineating the nature and size of the mass and excluding hepatic and peritoneal metastasis, this allows the treating surgeon to evaluate the resectability and any extension of the tumor to other parts of the pancreas. The features of IPMNs shown by CT include a dilated main pancreatic duct, cysts of varying sizes, and possibly mural nodules (fig. 1). Multiplicity of cysts and associated downstream dilatation of the main pancreatic duct, when present, distinguish IPMNs from other cystic pancreatic neoplasms.

Pancreatography by endoscopic retrograde (ERCP) or magnetic resonance and endoscopic ultrasonography (EUS) are important secondary diagnostic tools for evaluation of patients with suspected IPMN. Pancreatogra-

phy may allow for localization of mural nodules and pre-treatment classification of suspected branch- or main-duct types of IPMN. During ERCP, the finding of viscous fluid oozing from a patulous ampulla of Vater is a classic endoscopic finding in patients with IPMN (fig. 2). EUS enables evaluation of pancreatic ducts and assessment of both the fluid and solid components within. Aspirated fluid is classically viscous, clear and contains mucin. Cytological studies demonstrate mucin-rich fluid with variable cellularity: columnar mucinous cells with variable atypia may also be seen.

Tumor markers are of variable utility, and there is no strong evidence in the literature that tumor markers in aspirated fluid are useful in determining the degree of malignancy of IPMNs. The levels of amylase and carcinoembryonic antigen may be high, but CA 19-9 and CA 125 levels may be low.

Intraoperative ultrasonography is of unclear utility in assessing these pancreatic lesions. However, intraoperative pancreatoscopy is used increasingly to inspect the ductal system of the remaining pancreas, as described below.

Pancreatectomy for IPMN

Partial pancreatectomy is the cornerstone treatment for main-duct and some symptomatic large (>3 cm) branch-duct IPMNs of the pancreas. However, the opti-

Fig. 2. Viscous fluid oozing from a patulous ampulla of Vater in a patient with IPMN of the pancreas.

mal extent of pancreatic resection for some patients remains an open question. Most pancreatic surgeons recommend partial (usually right) pancreatectomy with the knowledge that the disease is most often located in the right side of the gland even though ductal changes may extend to involve other parts of the pancreas. Partial pancreatectomy also avoids the brittle diabetes that accompanies total pancreatectomy. Left (distal) pancreatectomy is the treatment of choice for the less common IPMNs that appear to be confined to the body and tail of the pancreas. Central pancreatectomy, or 'median pancreatectomy', has been performed by some for removal of localized tumors (likely branch-duct type) of the neck of the pancreas, but this has been associated with a higher incidence of pancreatic fistulas postoperatively and a higher tumor recurrence rate of 40% [20]. Total pancreatectomy is described for treatment of diffuse IPMNs of the pancreas. Although some investigators continue to advocate total pancreatectomy for the treatment of any IPMNs, evidence supporting this is decreasing with longer follow-up of patients treated by both R0 and R1 partial pancreatectomy. Most surgeons recommend partial pancreatectomy but discuss the management of the pancreatic margin with the patient preoperatively and counsel that approximately 15% of patients will require conversion to total pancreatectomy in order to achieve negative parenchymal resection margins [2].

At most institutions, surgical margins are assessed intraoperatively, with additional margins obtained for carcinomas in situ. Intraoperative pancreatoscopy is currently utilized to inspect the ductal system of the remaining pancreas [21–24]. Macroscopic 'skip' lesions can be identified intraoperatively in the remnant pancreas by choledochoscopy. However, pancreatoscopy has some limitations: flat epithelium that looks normal on endoscopy can contain neoplastic changes. Unidentified occult multifocal disease has been proposed as the basis for recurrence of IPMNs in the remaining pancreas in patients who develop recurrent disease in the remnant pancreas, after macroscopic and microscopically complete (R0) resection of an ostensibly localized IPMN [6]. There is no evidence that any form of extended lymphadenectomy is indicated for patients undergoing pancreatectomy for IPMN or adenocarcinoma of the pancreas [24]. While the postoperative mortality rate varies from 0 to 5% at high-volume centers, overall postoperative complication rate following the resection of IPMNs is 30–50%. Delayed gastric emptying and intra-abdominal sepsis are the most common complications [5, 6]. The profile and frequency rates of complications in patients with IPMNs are not statistically different from those in patients with pancreatic ductal adenocarcinomas treated by pancreatectomy [6].

Table 1. Features and outcome of surgically treated IPMNs among various institutions

Institution	Year	n	Invasive IPMN, %	5-YS ^a %	LN %
Multi-institutional study (Korea) [8]	2005	208	24.5	52.1	3.8
Virginia Mason Medical Center [26]	2005	100	24	46	32
Johns Hopkins Hospital [6]	2004	136	38	43	54
Massachusetts General Hospital and Verona Hospital, Italy [2]	2004	140	41.6	60	41
Memorial Sloan Kettering Cancer Center [5]	2004	63	48	58	16
Multi-institutional centers (France) [25]	2002	73	70	67 ^b	

LN = Lymph node involvement.

^a 5-year survival for invasive-type IPMNs. ^b 5-year survival for stage I invasive-type IPMNs.

Outcome

Survival rates are generally better in patients with IPMNs than in patients with pancreatic ductal adenocarcinoma (table 1) [2, 5, 6, 8, 9, 25, 26]. Sohn et al. [6] analyzed a series of 136 patients with IPMN and found that the survival rates for patients with noninvasive IPMNs were 97% at 1 year, 94% at 2 years, and 77% at 5 years. When the group of patients with noninvasive IPMNs was further analyzed, no differences were seen in survival rates between patients with IPMN adenoma and borderline IPMNs. Furthermore, this analysis failed to show any survival difference among all three IPMN types (main-duct, branch-type, or mixed-type). On the contrary, there was a significant survival difference between patients with noninvasive IPMNs and invasive IPMNs. The 1-, 3-, and 5-year survival rates for patients with invasive IPMNs were 72, 58, and 43%, respectively ($p < 0.0001$). Therefore, survival appears to depend on the invasive component of the lesion.

Similar to the analysis by Sohn et al. [6], a study of 63 patients with IPMNs by D'Angelica et al. [5] reported disease-specific actuarial 5- and 10-year survival rates of 75 and 60%, respectively. Furthermore, the survival rates in patients with noninvasive IPMN were better than those in patients with invasive IPMNs (5-year survival of 91 vs. 58%, respectively, $p < 0.01$). Patients with tubular-type invasive IPMN (50%) had a worse outcome than those with tubular colloid IPMNs (73%, $p = 0.008$). Likewise, Jang et al. [8] found a significant difference in the 5-year survival rates in patients with adenomas: 93.5%, borderline tumors: 91.4%, noninvasive tumors: 84.7% and invasive tumors: 52% ($p = 0.003$). In addition, the 5-year disease-free survival rates in patients with adeno-

ma, borderline, noninvasive, and invasive IPMNs were 80.1, 78.5, 84.7, and 36.9%, respectively ($p = 0.001$). These authors also noted a significant difference in survival between the groups of patients with benign (92.6%) and malignant (65.3% IPMNs, $p = 0.006$). However, no survival difference was seen among patients with main-duct (79.8%), branch-duct (76.5%), and combined-type (80%) tumors ($p = 0.728$) [8]. On the other hand, Maire et al. [25] demonstrated in their multi-institutional French analysis of 73 IPMN patients that the overall 5-year survival in stage I invasive IPMN (67%) was more favorable than that in a matched group of pancreatic ductal adenocarcinoma patients (23%, $p < 0.001$). However, the authors showed that outcomes of locally advanced disease in both invasive-type IPMN and pancreatic ductal adenocarcinomas were similar [25]. Likewise, Wada et al. [26] reviewed their experience with 100 patients with IPMNs from Virginia Mason Center: a very high 5-year survival in patients with noninvasive IPMNs (100%) was noted, compared to those with invasive IPMN (46%, $p < 0.001$). When patients with invasive IPMNs ($n = 24$) were matched (by TNM staging) to a similar group with pancreatic ductal adenocarcinoma ($n = 24$), the survival trend in favor of patients with invasive IPMNs was not insignificant ($p = 0.110$) [26].

IPMNs generally follow an indolent course. Although the small number of patients analyzed in reported studies and the short follow-up time preclude accuracy in determining the recurrence rate, in general, the recurrence rate is approximately 50% in patients with invasive IPMNs who have either negative or positive surgical margins and 8–10% in patients with noninvasive lesions. Furthermore, disease in patients with IPMNs with a focus of invasive carcinoma typically recurs in a disseminated form

or at the pancreatic remnant. Noninvasive and originally benign IPMNs recur less often but can do so as an invasive adenocarcinoma locally or as disseminated disease. Thus, an R0 resection does not guarantee freedom from subsequent pancreatic remnant disease and, paradoxically, there are patients with noninvasive IPMN treated by R1 surgical resection who do not develop subsequent remnant recurrence.

As for pancreatic ductal carcinoma, pathological markers such as lymph node involvement, vascular invasion, and perineural invasion are associated with poor outcomes. That is, these findings are often seen in patients with aggressive, malignant tumors and locally advanced disease. Several studies have shown poor outcomes in patients with lymph node involvement. Although very few of their patients with IPMNs had a positive lymph node status and vascular and perineural invasion, D'Angelica et al. [5] demonstrated that positive lymph node status was associated with a poor outcome: the median survival in the 10 patients in their study with lymph node involvement was 29 months. Another study [6] revealed that, in patients with positive lymph nodes, the 5-year actuarial survival rate was 0%, compared to a rate of 85% in patients with negative lymph nodes.

It appears that local recurrence following pancreatectomy for invasive IPMNs may be high; however, this has not been extensively validated. In the series of Jang et al. [8], 36.1% of patients who underwent R0 resections for invasive IPMNs developed locoregional failure: R0 resections for invasive IPMNs were performed in 83.7% of patients who underwent partial pancreatectomy for invasive IPMN, with disease recurring in 36.1% after partial pancreatectomy and in 37.5% after total pancreatectomy. Of those who underwent R0 resections for invasive IPMNs, disease recurred in 36.1%, whereas disease recurred in only 1 patient out of the 7 (14.2%) who underwent R1 resection [8]. One would expect that the locoregional failure rate would be higher among patients with R1 resections, but surprisingly, disease recurred more commonly in the liver. On the basis of these findings, the authors suggested considering postoperative systemic chemotherapy.

Current Controversies

Understandably, controversy still exists regarding the extent of pancreatectomy that should be performed in patients with pancreatic IPMNs. On the one hand, given the sometimes diffuse nature of IPMNs, total pancreatec-

tomy would appear to be a logical choice, but on the other hand, total pancreatectomy is associated with a somewhat higher risk of postoperative complications and often results in brittle diabetes. Conversely, the favorable outcomes in patients with benign or borderline IPMNs who undergo partial pancreatectomy argue strongly against total pancreatectomy. Thus, in an effort to achieve a balance between competing goals of completeness of resection, and short- and long-term morbidity, most pancreatic surgeons recommend partial pancreatectomy followed by close surveillance.

It is also increasingly clear that not all patients with IPMN require operation. A recent consensus conference on guidelines has recommended observation for patients with small asymptomatic branch-duct IPMN (<3 cm) that has no associated nodularity [27]. A plan for watchful surveillance with delayed intervention in such patients is believed to be reasonable as the risks for malignancy with small, asymptomatic branch-duct tumors is low, most of the patients are elderly and the time required to develop invasive malignancy may be longer than their life expectancy [28, 29].

There is no defined role for adjuvant treatment of pancreatic IPMNs. The pattern of failure includes both local and distant (usually liver) sites and thus future studies of adjuvant chemotherapy and radiation treatment may be worthy of consideration.

In summary, although IPMNs of the pancreas are a separate group of pancreatic cystic tumors, the diagnostic workup is similar to that used for patients with more common pancreatic tumors. Partial pancreatectomy is still the standard of care for patients with main-duct IPMNs and symptomatic larger branch-duct disease. Older patients with asymptomatic, small branch-duct type IPMN without any ductal nodularity may be managed by careful monitoring and delayed intervention as needed. Patients with IPMNs have a more favorable outcome than patients with ductal adenocarcinomas of the pancreas.

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