Intraductal Papillary Mucinous Tumors of the Pancreas

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Cystic neoplasms of the exocrine pancreas are a small fraction of pancreatic tumors. Within that group of cystic neoplasms, intraductal papillary mucinous tumors (IPMTs) can be distinguished from mucinous cystic neoplasms, serous cystic neoplasms, and pseudopapillary cystic tumors. Awareness of IPMTs has increased since the World Health Organization classified these tumors as its own group in 1996. Because of their favorable prognosis, an extensive diagnostic workup for IPMTs should be performed in patients presenting with cystic lesions of the pancreas. This workup often leads to the diagnosis and the predominant tumor location and size, although the extent of the ductal changes can only be established by histopathology. Surgical resection is the therapy of choice for IPMTs. The type of resection depends upon the extent of the quantitative and qualitative ductal involvement. Total pancreatectomy is currently the treatment for an IPMT that comprises the entire main duct.

Introduction

Cystic neoplasms account for approximately 5% of primary malignancies of the pancreas [1]. Intraductal papillary mucinous tumors (IPMTs) of the pancreas are part of the cystic neoplasms. They form a clinicopathologic entity that is recognized with increasing frequency since their classification by the World Health Organization (WHO) in 1996 [2••]. Within the group of exocrine cystic neoplasms, IPMTs can be distinguished from mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs), and pseudopapillary cystic tumors (Frantz tumors).

Until 1996, IPMTs were described in case reports and in small series under various names including mucinous ductal ectasia [3], intraductal papillary hyperplasia [4], villous adenoma [5], intraductal cystadenoma [6], mucinous pancreatic tumor [7], intraductal papillary neoplasm [8], ductectatic mucinous cystadenoma and adenocarcinoma [9], mucin-producing carcinoma [10], intraductal papillary adenocarcinoma [11], and adenocarcinoma with a predominant intraductal component [12]. A pathognomonic sign for an IPMT is mucinous secretion through the papilla of Vater that can be observed endoscopically. However, some IPMTs are nonsecreting mucinous tumors.

The awareness of IPMTs has recently increased and often results in an extensive diagnostic workup to detect the tumor and distinguish it from a benign obstructive chronic pancreatitis. Pathologically, IPMTs are characterized by intraductal papillary proliferation of columnar epithelial cells with cytoarchitectural atypia and longitudinal spread in the ductal system, usually in the main duct or a large branch duct [13–15]. Increased mucin production and mucin retention in the ductal system lead to diffuse or segmental ectatic ducts caused by mucin retention, often producing pancreatitis-like symptoms [2••,14,16•,17•]. Twenty-five percent of patients with IPMTs present with recurrent pancreatitis, but these patients are on average older and lack a history of chronic alcohol abuse compared with other pancreatitis patients. The lesion is mainly found in the head and in the uncinate process of the pancreas and has the potential of malignant transformation [13,18,19].

Surgical resection is the therapy of choice for these tumors. The type of resection must be determined on the basis of the extent and quality (stage of neoplasia) of ductal involvement. For patients with an IPMT that comprises the entire main duct, the treatment is total pancreatectomy.

Overall, IPMTs have a favorable prognosis after adequate resection. Despite their slow growth, IPMTs have obvious malignant potential and a relatively poor prognosis when invasive carcinoma with lymph node metastasis has developed. Whether the prognosis at that stage of cancer is as dismal as that of ductal adenocarcinoma has not been determined. Early recognition and pancreatectomy are the mainstays of IPMT therapy. This review investigates the epidemiology, diagnosis, staging, and treatment for this specific pancreatic tumor.

Epidemiology of Intraductal Papillary Mucinous Tumors of the Pancreas

Patients with IPMTs present with symptoms that are similar to those of idiopathic chronic pancreatitis, including

Table 1. Epidemiology of patients with IPMTs of the pancreas

Patient characteristic	Amount	Studies
Sex, *male/female ratio*	1.4–2.13	[15,16•,19,20,46,47]
Age, *years*	60–70	[15,16•,19,20,46,47]
Abdominal pain, %	29–80	[2••,12,15,16,19,46,50,55]
Pancreatitis-like symptoms (episode of acute pancreatitis), %	14–54	[2••,13,15,16•,19,46,55]
Obstructive jaundice, %	8–18	[2••,13,15,16•,19]
Weight loss, %	10–48	[2••,13,55]
Alcoholic stool, %	8–43	[2••,13,15,55]
Diarrhea, %	21–40	[2••,13,15,19,55]
Diabetes, %	52–85	[15,19,20]

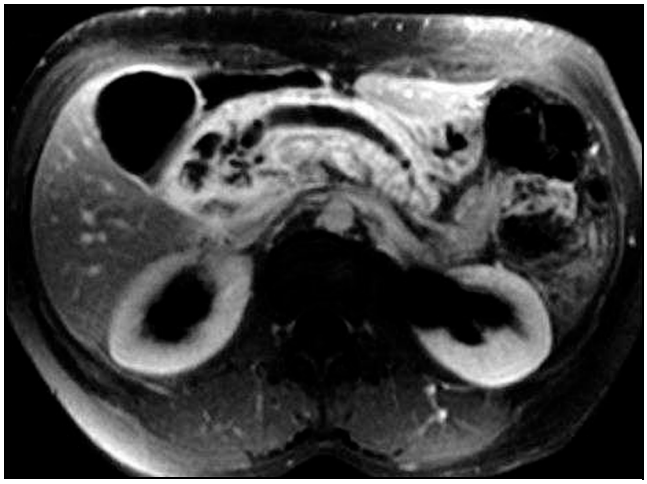

Figure 1. MRI of a patient with IPMT of the pancreatic head. Note characteristic dilation of the main duct and side branches.

abdominal pain, acholic stool, weight loss, diarrhea, and obstructive jaundice (Table 1). These patients show no pathognomonic findings in their history or physical examination. The lack of previous pancreatitis and the predisposing causative factors (alcohol) may be a tip-off to the astute clinician.

The mean age of patients with IPMT (64.9 years; range, 60–68) is typically two decades older than that of the usual patient presenting with chronic pancreatitis caused by alcohol abuse. The sex ratio is approximately 1.62 male/female (range, 0.75–3.00) [2••,13,14,16•,20]. This distinguishes IPMTs from MCNs, which mainly appear at a lower mean age (52.9 years) and occur predominantly in female patients (0.16 male/female ratio) [15,20]. Although these tumors typically arise in normal pancreatic parenchyma, diabetes mellitus coexists in 52% to 85% of patients [19].

Preoperative Diagnosis

The diagnosis of IPMT is usually suspected based on CT, ultrasound, or magnetic resonance imaging (MRI) but is virtually confirmed by endoscopic retrograde cholangiopancreatography (ERCP) showing mucus emanating from the papilla and a markedly dilated pancreatic main or branch duct filled with mucus. Preoperative staging should be performed by MRI or abdominal CT scan. In our opinion, ERCP is not absolutely necessary for preoperative staging because high-quality MRI and CT images can be quite characteristic for IPMT (Fig. 1) and MCN [21], but ERCP may confirm a questionable IPMT. Both tumors have considerable malignant potential, and patients with these tumors should be referred for surgery. Patients with main duct tumors and those with branch duct tumors with mural nodules or a tumor diameter of 30 mm or more may have a higher risk of developing invasive carcinoma [22]. A transpapillary intraductal pancreatic biopsy can sometimes be performed during ERCP to establish the preoperative diagnosis of IPMT. However, this procedure carries the risk of pancreatitis and bleeding, and a negative result does not rule out dysplasia or cancer (Table 2).

More detailed information on the stage and malignant potential of IPMT can be provided by endoscopic ultrasonography (EUS) performed by an experienced examiner. Criteria for malignancy include main duct tumors with the duct dilated 10 mm or more, branch duct tumors (>40 mm) with irregular septa, and large mural nodules (>10 mm) [23•].

Peroral pancreatoscopy and intraductal ultrasonography are investigational techniques that have been used to improve preoperative staging, especially to distinguish between benign and malignant variants of IPMTs [24]. The value of these techniques for clinical use, in particular the value of a negative examination, remains to be seen.

Intraoperative Pathologic Findings and Staging

Macroscopic findings

The predominant location for IPMTs is the pancreatic head, including the uncinate process. The tumor spreads longitudinally in the main duct and also frequently in the branch ducts. The ductal changes are characteristic for IPMTs and distinguish them from MCNs. Cystic lesions that are independent from the ductal system are more likely to be MCNs or serous cystic neoplasms [25]. Ductal

Table 2. Reported criteria of malignancy

Criteria	Examination	Studies
Tumor diameter, *cm*	Mean, 7.9 (range, 4.5–13.9)	[2••,14,15,16•,19,20]
Main duct diameter, *mm*	Mean, 17.05 (range, 3.9–70)	[2••,15,20,27,55]
Mural nodules (EUS)*	Mean diameter in 67% of patients with IPMTs: 24.8 mm	[15,20,27,46]

*Mural nodules are located in the wall of cysts. They are of epithelial nature, staining positive for vimentin, keratin, and epithelial membrane antigen, and they demonstrate a high proliferative rate.
EUS—endoscopic ultrasound.

dilation is clinically present in nearly all IPMT patients but not associated with tumor stage. Consequently, this neoplasm acquired the unusual name of "ductectasia" before the entity of IPMT was recognized.

Whether an intraoperative specimen contains a malignant or a benign variant (including borderline types) can be difficult to assess. Large diameters of the main duct or branch ducts are associated with malignancy (>20 mm). Furthermore, the ducts are filled with mucus, which is a characteristic and a prominent macroscopic finding in about 65% of patients with IPMTs [26]. Some branch duct IPMTs secrete their mucus into the main pancreatic duct and present themselves as main duct types.

Microscopic findings

IPMTs are classified by the WHO into three categories: 1) noninvasive lesions such as intraductal papillary–mucinous adenoma; 2) intraductal papillary–mucinous tumors with dysplasia (borderline and carcinoma in situ); and 3) invasive lesions such as intraductal papillary–mucinous carcinoma [16•]. This classification is based on tissue morphology, including the degree of dysplasia and the pattern of proliferation. The main differential diagnosis includes mucinous cystic neoplasms and ductal adenocarcinoma. In locally advanced IPM cancer (category 3), communication of the tumor with the pancreatic ducts, the presence of ovarian-type stroma, and capsular formations are key histologic factors to distinguish IPMTs from mucinous cystic tumors.

Further typical changes in IPMTs include papillary transformations of the ductal epithelium. Two kinds of papillary structures are pathologically described: an intestinal and a pancreatobiliary type. These two distinctive formations correlate with the progression to malignancy. Adenoma and borderline tumors are usually associated with the intestinal type of papillary transformation, whereas the pancreatobiliary type of transformation is seen more frequently in IPM cancer [2••]. The degree of papillary formation is important for classification of IPMTs. The papillary structures in the pancreatic ducts range from minimal, comprising only a few cells (30–40), to an extensive nodular formation in papillary tumors with diameter greater than 1 cm. This classification is represented in the WHO system [2••]. Transformation of IPMTs into aggressively spreading tumors is seen more often in the main duct or combined type than in branch duct lesions.

Invasive growth is usually minimal, and the tumors do not tend to spread extensively [15,27]. Often different grades of neoplasia can be observed within the same tumor, and the presence of hyperplasia, different stages of dysplasia, and carcinomatous epithelium in the same lesion is characteristic [2••]. The tumor itself provides a model of human pancreatic carcinogenesis and allows the investigation of genetic mutations during the progression to cancer.

Genetic Analysis and Future Diagnostic Potential

Diagnosis of pancreatic neoplasia using genetic markers is a new and promising target. Researchers around the world have looked intensively for specific markers of pancreatic neoplasia.

K-*ras* mutations and p53 overexpression

K-*ras* mutations and p53 protein overexpression are characteristically mutated in the majority of patients with pancreatic tumors (70%–100% and 30%–50%, respectively) [28•]. In patients with IPMTs, the prevalence of activating K-*ras* mutations is associated with site-specific histopathologic abnormality and correlates with tumor differentiation. The relative frequency of K-*ras* mutations in the progressive stages of IPMT is 16.7% in normal epithelium and papillary hyperplasia, 28.6% in low-grade dysplasia, and 57.1% in high-grade dysplasia, carcinoma in situ, and invasive carcinoma. This frequency is consistent with an important role of K-*ras* gene mutations in the transformation from normal epithelium to invasive carcinoma in the majority of patients with IPMTs (Fig. 2). Mutations leading to p53 inactivation may also be involved in this process. Mutations of the *p53* suppressor gene with subsequent detectable overexpression of the p53 protein have been correlated with the grade of malignancy in IPMT [28•,29,30].

The knowledge of early genetic events has not solved the problem of early detection. At least two thirds of our patients with pancreatic adenocarcinoma have metastatic tumors in their regional lymph nodes at the time of resec-

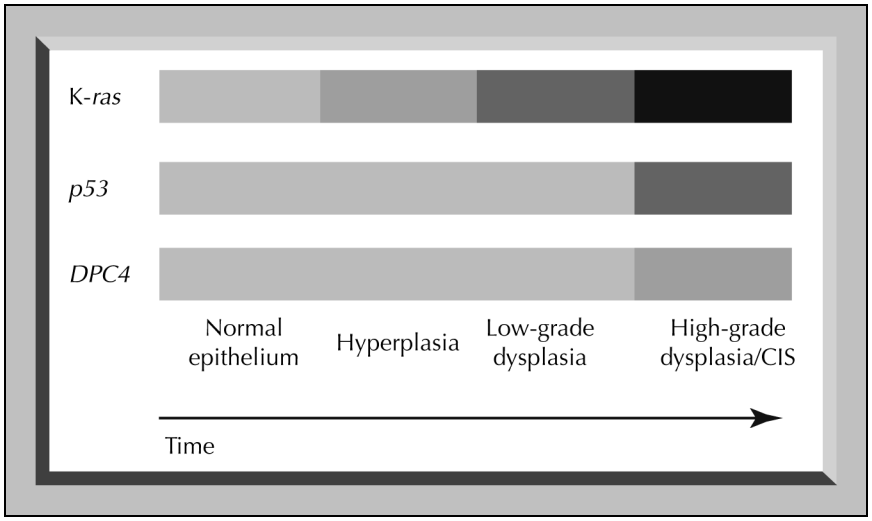

Figure 2. Schematic representation of the increasing prevalence of different genetic mutations as ductal epithelium evolves through stages of dysplasia to cancer in cystic pancreatic tumors. The sequence of events has been investigated in IPMTs and mucinous cystic neoplasms. CIS—carcinoma in situ.

tion, and a method to detect these tumors before they have spread to regional nodes is needed. However, studies using K-*ras* and p53 as markers to detect pancreatic tumors through analysis of blood and pancreatic juice have not been successful. The specificity of these mutations is low, and a clear diagnosis of malignancy is only possible in a few patients. For this reason, new targets are needed to identify early stages of pancreatic carcinogenesis, including specific mutations and protein transformations.

DPC4 protein

DPC4 (deleted in pancreatic cancer 4) is a tumor suppressor protein that is commonly mutated in pancreatic adenocarcinoma. DPC4 mutation with loss of function seems to be a late event because the cystic tumor progresses into an invasive cystic carcinoma. In a recent study, Sohn *et al*. [16•] showed that all noninvasive IPMTs have a normal *DPC4* gene. However, in invasive IPMT the expression of this gene is detected in 84% of patients [16•,25,31•,32]. Therefore, routine DPC4 analysis may improve the distinction between benign and malignant IPMT (Fig. 3).

Mucin expression

Mucin (MUC) is a membrane-associated glycoprotein. Two mucin immunophenotypes have been analyzed with respect to their relationship with this malignancy.

MUC2 is an intestinal secretory-type mucin, mainly expressed in goblet cells of the intestine. IPM-cancer with invasive growth and a poor outcome usually showed MUC1 positive staining without MUC2 expression. IPMT with expansive growth and a favorable outcome showed MUC1-negative staining and MUC2 expression [25,26,33,34].

Recently Nakamura *et al*. [35] evaluated a number of IPMT patients with MUC1-negative and MUC2-negative expression patterns. The incidence of carcinomatous change and invasive proliferation of the carcinoma in the MUC2-positive tumors was significantly higher than in the MUC2-negative tumors. Patients with MUC2-positive IPMTs tended to have a worse clinical outcome than patients with MUC2-negative IPMTs. Also, MUC2 expression may have an impact on the pattern of recurrence after surgical resection [36]. About half the MUC2-positive IPMTs showed involvement of the surgical margins, and these patients experienced a recurrence after surgery. MUC2-positive tumors seemed to have a greater potential for malignancy than MUC2-negative tumors. Distinct MUC2 staining in neoplastic and nonneoplastic epithelium may be useful to assess the tumor-free surgical margins in IPMTs with relatively high malignant potential [36]. The differences in mucin expression patterns, morphologic appearance, and potential malignancy suggest that two different neoplastic lineages can be recognized within the entity of IPMT.

Telomerase activity

Telomerase is an important enzyme found in tumor cells. In normal cells its physiologic function is to regulate the length of telomeres. Telomerase has significantly increased enzyme activity in cancer compared with normal tissue.

Telomerase activity in pancreatic juice as a measurement for malignancy in ductal adenocarcinoma has been reported in several studies [37]. Preoperatively, malignant and benign IPMTs are difficult to distinguish. Therefore the usefulness of preoperative staging with telomerase activity, measured by the so-called TRAP (telomerase repeat amplification protocol) assay, was investigated [38]. The results point to a higher sensitivity (85%) and specificity (100%) of telomerase activity in malignant IPMTs than cytologic staining. For this reason, telomerase activity may become a prognostic and diagnostic target [38].

Büchler *et al*. [39] have shown that real-time quantitative polymerase chain reaction (PCR) is even more specific than the TRAP assay in detecting telomerase activity in pancreatic cancer tissue. Real-time PCR revealed a consistently high level of telomerase activity in well-differentiated (Capan-1 and Capan-2) as well as undifferentiated (PANC-1 and MIA-PaCa-2) cell lines. An undifferentiated tumor has higher

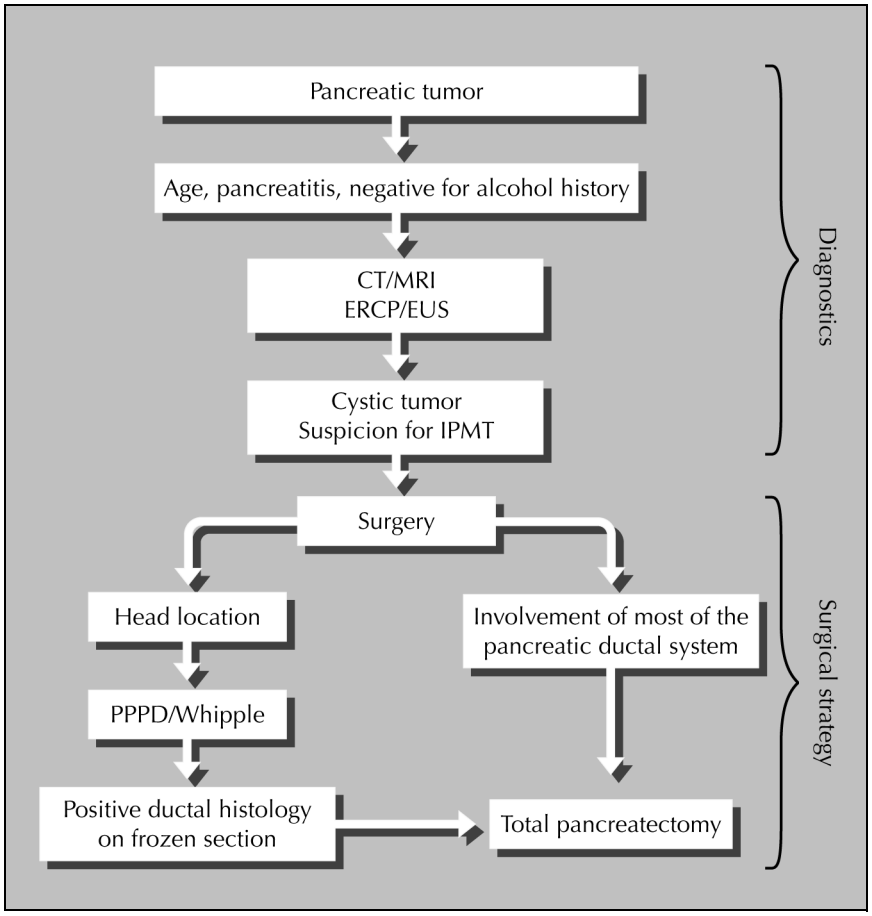

Figure 3. Algorithm of the diagnostic and surgical strategy for patients with IPMTs. PPPD—pylorus-preserving procedure.

telomerase activity than a well-differentiated tumor. Light cycler technology may be an efficient way to standardize tumor grading by measurement of telomerase activity in pancreatic juice, biopsies, or surgical specimens.

Therapy

Surgical treatment

The treatment of choice for tumors of the head of the pancreas, the typical location of IPMT [40], is radical pancreatoduodenectomy based on the specifications of an international workshop on surgical procedures in 1998 [37,41,42]. Whether it should be performed as a pylorus-preserving procedure or as the classical Kausch-Whipple operation is still debated. A recent randomized study demonstrates the advantages of the pylorus-preserving procedure in the short term without loss of cure rates [43]. The intra- and postoperative mortality has decreased to less than 5% in specialized centers [44]. Because many of the IPMTs are benign or borderline tumors with a relatively low growth rate, the safety of the operation is critical for the concerned patient. The main complications after pancreatic resection are pancreatic fistula, hemorrhage, and delayed gastric emptying. Although the majority of postoperative complications do not necessitate reintervention or are manageable by interventional drainage, the safety and low morbidity of pancreatic resection for benign disease is crucial. With respect to survival, the pancreatic head resection demonstrates excellent outcome for patients with IPMTs of this type. Concentration of these operations in centralized units improves the quality of operative and preoperative management and survival [44].

The characteristic biology that distinguishes IPMTs from serous cystic and mucinous cystic neoplasms must be considered in surgery for IPMTs. Whereas preoperative studies allow the surgeon to locate serous and mucinous cystic neoplasms accurately and to plan a limited pancreatic resection accordingly, this is not always the case in IPMTs. The tumors arise and can spread through the entire ductal system [45]. The macroscopic location of this tumor may just be "the tip of the iceberg," with hyperplasia and different degrees of dysplasia present in the ductal system and outside of the planned line of resection. Patients with IPMTs need to be informed of the possibility of a total pancreatectomy with the consequence of endocrine and exocrine pancreatic insufficiency.

The rationale for this treatment derives from the studies discussed previously. The ductal system seems to have a functional defect and acquires genetic mutations that are correlated with different stages of neoplasia. Any form of remaining IPMT at the resection line may progress to local

recurrence and invasive cancer over time. IPMTs are best treated by total pancreatectomy, although lesser subtotal resections should be strongly considered depending on patient age, medical comorbidity, and psychosocial concerns.

Partial pancreatic resection should be supported by an intraoperative frozen section that shows disease-free margins [46]. In patients with invasive IPMTs, a lymphadenectomy should be added, and total pancreatectomy may often be necessary [37]. Patients with IPMTs have a favorable prognosis if radical resection can be performed [37,47,48].

In side branch tumors, the risk of malignancy is low, especially when the tumor is smaller than 3 cm and has no solid components. Some authors have proposed nonoperative management for elderly patients, arguing that most of them are asymptomatic and that the time required to develop invasive malignancy may be greater than their life expectancy [49,50]. Thus, treatment of patients with IPMTs needs to be individualized and carefully planned. Total pancreatectomy may be appropriate in a healthy patient with an invasive IPMT that is extending into the body and tail of the gland.

Follow-up and Long-term Survival

Patients with IPMTs have a favorable prognosis after adequate resection. Despite their relatively slow growth and evolution into malignant neoplasm, IPMTs have obvious malignant potential and a poor prognosis when invasive carcinoma has developed. The 3-year survival rate is reported as 80% to 95% for all histologic types of IPMT, but it decreases to 55% to 76% if malignancy has developed [35,46,51••,52–55].

At present, there is no universally accepted concept of follow-up. In patients with benign or borderline malignant IPMTs, no formal follow-up is needed. Patients have excellent outcomes and should only be restaged if they are symptomatic. In these instances, local (technical) problems may be the source of new symptoms, such as a narrow pancreatojejunostomy that results in bouts of acute pancreatitis. After resection of invasive IPMTs, particularly in patients with lymph node metastasis, we recommend follow-up in intervals of 4 to 6 months for the first 2 years and yearly thereafter. CT or MRI is the best method for follow-up.

In rare patients, dysplasia remains at the resection line. This can occur when the intraoperative frozen section produces a negative result and the final pathologic assessment detects dysplasia. The resection is therefore incomplete. Completion of pancreatectomy should follow in patients with dysplasia. Follow-up every 6 to 12 months may be an alternative in patients with low-grade dysplasia.

Conclusions

IPMTs have a favorable prognosis after adequate resection. Despite their slow growth, IPMTs have obvious malignant potential and a relatively poor prognosis when invasive carcinoma with lymph node metastasis has developed. IPMTs are best treated with total pancreatectomy, although lesser subtotal resection should be considered depending on patient age, medical comorbidity, and psychosocial concerns. Intraoperatively, the extent of resection depends on the result of frozen section examination. Dysplastic lesions at the resection margin usually lead to total pancreatectomy (Fig. 3). Because of the potential to modify and extend the surgical resection at the time of surgery, it is important for the surgeon to discuss the risks and consequences of a total pancreatectomy with the patient. A structured follow-up is recommended in patients with invasive IPMTs.

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