Surgical Management of Intraductal Papillary Mucinous Tumors of the Pancreas

The Role of Routine Frozen Section of the Surgical Margin, Intraoperative Endoscopic Staged Biopsies of the Wirsung Duct, and Pancreaticogastric Anastomosis

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Hypothesis: Resection of intraductal papillary mucinous tumors of the pancreas (IPMTP) should be tailored to longitudinal spreading into the pancreatic ductal system and the presence of malignant transformation.

Objective: To review a single institutional experience with IPMTP, focusing on the operative strategy of tailoring resection to the extent of disease.

Design: Retrospective study.

Setting: Academic tertiary referral center.

Patients: Thirteen patients with IPMTP were referred for resection during the past 10 years. Malignant growth was present in 7 patients (54%). According to the determination of tumor extent, distal pancreatic resection was performed in 3 patients, pancreatoduodenectomy was done in 9 patients, and total pancreatectomy was performed in 1 patient. The median follow-up time in this series was 46 months (range, 3-104 months).

Main Outcome Measures: Preoperative and perioperative diagnosis, final pathologic results, and long-term outcome.

Results: A correct preoperative or perioperative diagnosis of IPMTP was achieved in 9 patients (69%). Routine frozen section of the surgical margin was used in all patients, changing the operative strategy in 3 (23%) of 13 patients by extending resection or leading to total pancreatectomy in 2 patients and 1 patient, respectively. A perioperative endoscopic examination of the Wirsung duct was performed in 3 patients with a correct preoperative or perioperative diagnosis of IPMTP and a dilated pancreatic duct. This allowed the examination of the entire pancreatic ductal system and staged intraductal biopsies, changing the operative strategy in 1 of these patients. Finally, after pancreatectoduodenectomy, pancreaticogastric anastomosis was constructed in 5 patients, allowing endoscopic assessment of the pancreatic stump during long-term follow-up. The 5-year actuarial survival rate was 56.8% in the whole series. All patients with benign or microinvasive malignant disease remained disease-free, whereas all patients with invasive malignant disease died of tumor recurrence.

Conclusions: Accurate determination of the extent of ductal disease and residual malignant growth, when present, is critical during surgical exploration to achieve radical resection and cure. Operative strategy should be based on routine frozen section of the surgical margin and perioperative endoscopic examination of the Wirsung duct with staged intraductal biopsies when technically feasible. The routine use of pancreaticogastric anastomosis after pancreatectoduodenectomy allows easy, safe, and efficient long-term endoscopic assessment of the pancreatic stump.

Arch Surg. 2001;136:1256-1262

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PATIENTS AND METHODS

During a 10-year period, 13 patients with IPMTP were referred to our department for surgical resection. There were 8 men and 5 women, with a mean age of 62 years (median, 65 years; range, 46-74 years). Two patients (15%) were high risk and were classified as level III by the American Society of Anesthesiologists. Clinical indications included incidental discovery (1 patient), isolated abdominal pain (2 patients), abdominal pain and jaundice (1 patient), abdominal pain and mass (1 patient), repeated attacks of acute pancreatitis (5 patients), steatorrhea with weight loss (1 patient), and painful chronic pancreatitis (2 patients). Type 2 diabetes mellitus and steatorrhea were present in 23% and 31% of the patients, respectively. The mean duration of symptoms was 29 months (median, 8 months; range, 1-132 months). In 5 patients (38%), the initial diagnosis was chronic pancreatitis; the period needed to show the accuracy of this diagnosis was 43 months (median, 23 months; range, 8-132 months). The final preoperative diagnosis was IPMTP in 8 patients (61%), pancreatic duct cell carcinoma in 3 patients, and pancreatic cystadenocarcinoma in 2 patients. A correct diagnosis was given in 1 of these patients after the use of frozen section. Plasma levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were useless to discriminate between benign and malignant forms of the disease. All patients were examined preoperatively using computed tomography and endoscopic retrograde cholangiopancreatography (ERCP). Magnetic resonance cholangiopancreatography (MRCP) was performed in 8 patients (61%), and endoscopic ultrasonography (EUS) was done in 10 patients (77%). Endoscopic cytologic brushing was performed in 9 patients (69%), providing true-positive results for benign and malignant disease in 4 patients each (accuracy, 89%) and a false-negative result for malignant disease in 1 patient. The main tumor was located in the head of the pancreas in 7 patients (54%), in the uncinate process in 3 patients (23%), and in the body or tail of the pancreas in 3 patients (23%). According to the classification by Furukawa et al, 4 tumors were type 1, 3 were type 2, 2 were type 3, and 4 were type 4.

During the surgical procedure, the extent of resection was determined by careful attention to preoperative ERCP examinations and by intraoperative ultrasound (Figure 1) in all patients. A perioperative endoscopic examination of the Wirsung duct (Figure 2) was performed in 3 patients (1 with type 1 and 2 with type 4 IPMTP according to Furukawa et al) for whom a correct preoperative or perioperative diagnosis was obtained. In the remaining patients, this procedure was not performed because the correct diagnosis of IPMTP was made only during the final pathological examination or because the main pancreatic duct was not sufficiently dilated. The examination was performed with flexible scopes (external diameter, 3.3 mm or 4.9 mm; Olympus, Tokyo, Japan) according to the size of the pancreatic duct. Biopsy forceps were used through the operative channel of the 4.9-mm scope to perform staged intraductal biopsies within the pancreatic ductal system. These biopsies were sampled from the transection line following pancreatic transection to the tail of the pancreas during pancreatoduodenectomy (Figure 3). In all patients, frozen section was used for endoscopic staged biopsies of the Wirsung duct and for the pancreatic surgical margin.

All patients had long-term follow-up with clinical, biochemical, and radiological assessment. In the 10 surviving patients, MRCP and EUS were performed in 10 and 4 patients, respectively. In the 3 patients with a follow-up time longer than 1 year and who underwent pancreaticogastric anastomosis following pancreatoduodenectomy, the pancreatic remnant was assessed using EUS and ERCP with cytologic brushings of the pancreatic duct. The remnant was opacified by direct cannulation or by puncture using EUS. Samples of pancreatic juice were obtained for cytological examination. Survival curves were calculated according to the Kaplan-Meier actuarial method.

RESULTS

During the final pathological examination, IPMTP was confirmed in all patients. Malignant growth was present in 7 patients (54%), with microinvasive and invasive carcinoma in 4 and 3 patients, respectively. Two of our patients had an oncocyty variant of IPMTP. Intraoperative findings, surgical procedures, and pathological features of the patients are reported in Table 1.

According to tumor location, pancreatoduodenectomy was performed in 9 patients, total pancreatectomy including mesenteric venous reconstruction was performed in 1 patient, and distal pancreatectomy was done in 3 patients. Frozen section at the transection line was negative for dysplasia in 10 patients and positive for benign papillary hyperplasia in 1 patient. In the latter, 2 additional pancreatic sections were carried out, but the frozen section showed a persistent benign form of the disease. Therefore, the resection was not extended forward, and a pancreaticogastrostomy was performed to assess the pancreatic stump during long-term follow-up. In 1 patient each, frozen section at the surgical margin indicated the presence of severe dysplasia and in situ carcinoma. In 1 of these 2 patients, 3 additional pancreatic resections were performed until a negative surgical margin was obtained to allow a pancreatoduodenectomy with pancreaticogastric anastomosis. The last patient exhibited persistent signs of malignant growth at the surgical margin despite repeated additional pancreatic resections. A total pancreatectomy was carried out in association with the reconstruction of the mesenteric vein by using a jugular venous graft (Figure 4). Overall, the routine use of frozen section of the surgical margin modified surgical treatment in 3 (23%) of 13 patients.
In 1 patient with a type 1 tumor and in 2 patients with a type 4 tumor according to the classification by Fukuwaka et al,7 in whom a correct preoperative and perioperative diagnoses of IPMTP were done, endoscopic staged biopsies of the Wirsung duct were performed after the completion of a pancreatoduodenectomy, indicating that the distal pancreatic duct system was free of disease. The mean number of these staged endoscopic biopsies was 4 (range, 3-5). In 1 patient with uniformly negative staged biopsies in the distal pancreatic ductal system, pancreaticoenteric anastomosis was performed using a pancreaticogastrostomy after the completion of a pancreatoduodenectomy (Figure 5). In the other patient, perioperative staged biopsy specimens were positive for papillary hyperplasia in the pancreatic neck, whereas the pancreatic duct within the body and tail of the pancreas was normal, leading to the extension of the resection until a normal pancreatic duct was found. In the remaining patient with associated calcified chronic pancreatitis, intraoperative endoscopic examination of the Wirsung duct demonstrated intraductal stones in the extreme tail of the pancreas that were inaccessible for endoluminal lithotripsy; this led to associated short distal pancreatic resection.

No operative or hospital mortality was observed in this series. Postoperative complications occurred in 5 patients (38%) and included transient pancreatic fistula in 3 patients and hemorrhage from the transection line in 2 patients, requiring radiological embolization and reoperation in 1 patient each. The mean postoperative hospital stay was 18 days (median, 17 days; range, 10-31 days).

The mean follow-up period was 45 months (median, 46 months; range, 3-104 months). The 5-year actuarial survival rate was 56.8% in the whole series, 100% in the group of patients with benign disease, and 27.8% in the group with malignant disease. At a mean delay of 41 months (median, 52 months; range, 12-59 months), all 4 patients with invasive carcinoma died of disease recurrence. The 4 patients demonstrating microinvasive carcinoma are all alive after a mean delay of 41 months (median, 38 months; range, 3-86 months), with no sign of disease recurrence on radiological studies. Finally, the 6 patients with a benign form of the disease are alive and disease-free at a mean delay of 49 months (median, 51 months; range, 3-104 months). The patient with benign residual dysplasia at the surgical margin remains disease-free 13 months postoperatively, with no sign of recurrence on MRCP- and EUS-guided cytologic brushings and biopsies.
Intraductal papillary mucinous tumors of the pancreas show completely different clinicopathological features from classical pancreatic duct cell carcinoma.\(^{10,12,27,29}\) The specific characteristics of IPMT include (1) massive mucin production and mucin retention in the pancreatic ductal system; (2) the longitudinal spread of papillary neoplasms within the pancreatic ductal system; and (3) the potential for malignant transformation\(^{10,12,19,27,29}\) with sequential changes from hyperplasia, via adenoma, to in situ carcinoma and finally invasive carcinoma.\(^{5,7,10,20,29}\)

This particular disease tends to spread intraductally, either as polypoid lesions with mural nodules or as flat lesions with micropapillary studding of the epithelial lining.\(^{3,7,14,27,30}\) The disease is predominantly located in the head of the pancreas, especially in the uncinate process.\(^{4}\) However, diffuse forms of IPMT have been reported\(^{†}\); these forms have been encountered in 7% to 8% of cases\(^{12,19,21,30}\) up to between 21% and 29%.\(^{21,28}\) Multifocal forms of the disease have also been observed,\(^{4,8,11,15,20}\) at rates of 20.8% by Kaneko et al\(^{12}\) and 32% by Fujii et al.\(^{11}\)

Whether or not preoperative imaging studies are useful for diagnosing IPMT, these techniques are still unable to accurately discriminate between benign and malignant forms of the disease\(^{14,19,21,27}\) unless transpapillary endoscopic cytologic examination of the pancreatic juice is used.\(^{7,12}\) However, the diagnosis of malignant disease cannot be completed until the full specimen is available for pathological examination.\(^{23}\)

This disease has a good prognosis, even in cases of noninvasive carcinoma. During surgical exploration, the surgeon must be able to accurately assess the intraductal spread of the disease to achieve a radical resection. Even using ERCP, the most accurate procedure, a diffuse dilatation of the pancreatic duct may be due to obstruction by tumor growth or by mucous plugging produced by a tumor located solely in the head of the pancreas, or to a tumor diffusely involving the pancreatic duct.\(^{21}\) To establish an accurate perioperative staging of the disease, we emphasize the importance of using intraoperative ultrasound, intraoperative endoscopic examination of the Wirsung duct with multiple staged ductal biopsies, and pathological examination using rou-

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**Figure 3.** Intraoperative endoscopic examination of the Wirsung duct in the body and tail of the pancreas following pancreatoduodenectomy. **A,** Normal macroscopic aspect of the pancreatic duct. **B,** Frozen section demonstrated the presence of benign dysplasia at the transection line. After additional pancreatic resection, pancreatico gastric anastomosis was performed.

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\(^{†}\)References 6, 12, 19, 21, 24, 27, 28, 30-35.
of multiple staged ductal biopsies to detect microscopic lesions of IPMTP, with the possibility of obtaining better histologic specimens with optical control. Therefore, intraoperative endoscopic examination of the Wirsung duct appears to be important for diagnosing intrapancreatic duct extent and multicentric lesions of IPMTP. Finally, the use of this procedure combined with staged ductal biopsies provided important information for designing the operative strategy so that appropriate and curative pancreatic resections could be performed. In the study by Kaneko et al, an additional pancreatic resection was performed in half of the patients in whom occult IPMTP lesions were detected by intraoperative endoscopic examination of the Wirsung duct. In our experience, the endoscopic Wirsung duct examination was safe and easy to perform with a standard flexible ureteroscope. This procedure affected operative treatment in 1 of the 3 patients in whom it was used.

Because the extent of ductal involvement may be difficult to determine prior to surgery, the importance of confirming the pancreatic margin to be tumor-free by frozen section pathological examination has been highlighted by many authors.22-24,27,28,30 The presence of papillary lesions at the surgical margin is frequent in IPMTP and was reported in the literature in 42 (38%) of 110 patients (Table 2). There is no doubt that the presence of malignant growth at the pancreatic duct margin requires an extension of the resection up to a total pancreatectomy,14-20,28 as we performed in 1 of our patients. The negative effect on patient survival of omitting routine frozen section of the surgical margin was demonstrated in the study by Sho et al; 43% of the patients experienced local recurrence, suggesting an incomplete resection. In this series, only 1 of 4 patients re-explored surgically with the aim of curative resection was able to undergo the operation. In cases of microscopic benign dysplastic lesions at the pancreatic margin, the optimal surgical strategy remains controversial. Traverso et al30 and Sugiyama and Atomi31 reported completion of total pancreatectomy in 24% and 29% of their patients, re-

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**Figure 4.** Frozen section pathological examination of the surgical margin in a patient with malignant intraductal papillary mucinous tumors of the pancreas who underwent pancreatoduodenectomy. Persistence of in situ carcinoma and severe dysplasia at the surgical margin led to total pancreatectomy.

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**Table 2. Intraoperative Findings, Surgical Procedures, and Pathological Features of 13 Patients Undergoing Resection for IPMTP**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Location of Tumor Within the Pancreas</th>
<th>Final Pathological Results</th>
<th>Type of Carcinoma</th>
<th>Timing of IPMTP Diagnosis</th>
<th>Frozen Section of Surgical Margin</th>
<th>No. of Additional Pancreatic Resections</th>
<th>Final State of Surgical Margin</th>
<th>Type of Pancreatic Resection</th>
<th>PGA</th>
<th>Follow-up, mo</th>
<th>Clinical State at Follow-up</th>
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<tbody>
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<td>1</td>
<td>Head</td>
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<td>Pathological</td>
<td>N</td>
<td>0</td>
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<td>59</td>
<td>D2</td>
<td>S1</td>
</tr>
<tr>
<td>2</td>
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<td>Preoperative</td>
<td>N</td>
<td>0</td>
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<td>PDR</td>
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<td>104</td>
<td>S1</td>
<td>S1</td>
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<td>DP</td>
<td>...</td>
<td>56</td>
<td>S1</td>
<td>S1</td>
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<td>N</td>
<td>0</td>
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<td>DP</td>
<td>...</td>
<td>70</td>
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<td>S1</td>
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<td>M</td>
<td>2</td>
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<td>52</td>
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<td>PDR</td>
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<td>56</td>
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<td>S1</td>
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<tr>
<td>8</td>
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<td>B</td>
<td>Preoperative</td>
<td>N</td>
<td>0</td>
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<td>PDR</td>
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<td>46</td>
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<td>B</td>
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<tr>
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<td>PDR</td>
<td>Yes</td>
<td>3</td>
<td>S1</td>
<td>S1</td>
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</table>

*IPMTP indicates intraductal papillary mucinous tumors of the pancreas; PGA, pancreaticogastric anastomosis; M, malignant; N, normal; PDR, pancreatoduodenal resection; D2, death with recurrence; B, benign; S1, survival without recurrence; DP, distal pancreatectomy; TP, total pancreatectomy; SD, severe dysplasia; and ellipses, not applicable.*
respectively. On the other hand, researchers at Erasme University Hospital (Brussels, Belgium)\textsuperscript{19,22} reported the presence of benign dysplasia at the surgical margin in 57\% of their patients in whom a total pancreatectomy was never performed; 1 patient experienced a recurrence in the remaining pancreas 66 months after a distal pancreatectomy. Because of the increased mortality rate\textsuperscript{23} and severe, irreversible functional sequelae associated with total pancreatectomy, the authors suggested that the role of frozen section should be limited to ruling out malignant growth at the surgical margin and that total pancreatectomy would not be performed in cases of benign disease discovered during frozen section pathological examination of the surgical margin.\textsuperscript{22} Because the disease is often diffuse or multicentric, the surgeon cannot rely only on the surgical margin to determine the extent of resection to prevent recurrent symptoms. We believe that routine frozen section and intraoperative endoscopic staged biopsies of the Wirsung duct can be used as complementary tools to achieve accurate assessment of ductal extent in patients with IPMTP.

Finally, the use of pancreaticogastric anastomosis after pancreatoduodenectomy in patients with IPMTP has seldom been reported.\textsuperscript{23} This reconstructive technique permits direct access to the pancreatic stump by endoscopy during long-term follow-up, allowing direct opacification of the pancreatic duct and a sampling of pancreatic juice for cytological examination. Even in cases where stricture of the pancreaticogastrostomy impairs direct access to the pancreatic duct, the use of EUS allows a precise examination of the pancreatic ductal system as well as puncture for cytological examination, as we performed in 1 of our patients. In our experience, the difficulty of accessing the pancreaticogastric anastomosis reported by Navarro et al\textsuperscript{23} was never encountered. To improve the long-term oncological follow-up of patients with IPMTP treated with pancreatoduodenectomy, we recommend the performance of pancreaticogastric anastomosis as a routine reconstructive procedure.

In conclusion, IPMTP is a disease with a good prognosis, even in cases of noninvasive malignant transformation. Accurate determination of ductal disease extent is critical during surgical exploration to achieve radical curative resection. In patients who have predominant cephalic IPMTP with a dilated pancreatic duct, routine frozen section pathological examination of the surgical margin and endoscopic examination of the Wirsung duct with staged biopsies should be used to allow precise macroscopic and microscopic diagnosis of the extent of ductal disease. In patients who have IPMTP treated with pancreatoduodenectomy, the routine use of pancreaticogas-

<table>
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<th>Author</th>
<th>No. of Patients</th>
<th>Benign Dysplasia at the Surgical Margin, No. (%)</th>
<th>Mean Duration of Follow-up, mo</th>
<th>Recurrence at the Pancreatic Stump, No. (%)</th>
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<td>11 (41)</td>
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<td>26</td>
<td>5 (19)</td>
<td>24</td>
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</table>

*IPMTP indicates intraductal papillary mucinous tumors of the pancreas.
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REFERENCES