

Intraoperative irrigation cytology of the remnant pancreas to detect remnant distinct pancreatic ductal adenocarcinoma in patients with intraductal papillary mucinous neoplasm undergoing partial pancreatectomy

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Background. Patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas may have concomitant distinct pancreatic ductal adenocarcinoma (PDAC). We evaluated the safety and usefulness of intraoperative irrigation cytology of the remnant pancreas (IICP) during pancreatectomy to detect remnant distinct PDAC in patients with IPMN.

Methods. The records of all 48 patients with IPMN who underwent IICP during partial pancreatectomy at our institution from April 2007 to March 2012 were reviewed retrospectively. After division of the pancreas, a 4-French tube was inserted into the main pancreatic duct of the remnant pancreas from the cut edge, and fluid for cytologic examination was obtained by saline irrigation through the tube. If the third IICP was positive, patients underwent additional pancreatic resection. Clinical and pathologic outcomes were evaluated.

Results. The third IICP was positive in 5 patients. Postoperative pathologic examination showed that these patients all had remnant distinct PDAC in the additionally resected specimen, which was not detectable on preoperative imaging examination or on intraoperative macroscopic examination, ultrasonography, or palpation. This PDAC was stage 0 in 4 patients and stage III in 1 patient. No procedure-related complications were observed. One patient developed peritoneal metastasis after 10 months, 1 developed liver metastasis after 20 months, and 1 developed PDAC in the remnant pancreas after 24 months.

Conclusion. IICP seems to be a safe and useful method for detection of early stage PDAC concomitant with IPMN that cannot be detected by preoperative imaging or intraoperative examination. (Surgery 2014;155:67-73.)

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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN) of the pancreas was first reported by Ohashi et al¹ in

1982. Since then, improved imaging techniques and increased clinician awareness have increased the frequency of diagnosis.² International consensus guidelines established in 2006³ and revised in 2012⁴ defined appropriate management. Histologic findings range from low-grade dysplasia to invasive ductal carcinoma, but progression to carcinoma is generally slow⁵⁻⁷ and the prognosis is therefore favorable. In contrast, the prognosis for pancreatic ductal adenocarcinoma (PDAC) remains poor. Early diagnosis can improve prognosis,

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but early PDAC is generally asymptomatic and difficult to detect on imaging examinations, and the majority of patients present with advanced disease. The reported prevalence of PDAC in patients with IPMN, including both synchronous and metachronous lesions, is 4.4–9.9%,^{8–15} indicating that patients with IPMN have an increased risk of PDAC.

Because of the increased risk of PDAC, we performed intraoperative irrigation cytology of the remnant pancreas (IICP) during some partial pancreatectomy procedures in patients with IPMN. From April 2007 to November 2010, IICP was performed at the discretion of the surgeon. Postoperative pathologic examination found that 13 of the 37 patients (35%) who did not undergo IICP during this period had malignant IPMN or unexpected distinct PDAC in the resected specimen despite negative preoperative cytology. We also previously reported a patient with IPMN who had concomitant multifocal PDAC that was not detectable on preoperative imaging examinations.¹⁶ We therefore changed our policy, and from December 2010 we performed IICP during partial pancreatectomy in patients with IPMN whenever feasible, aiming to detect remnant, distinct PDAC. Such a protocol has not previously been reported. This study evaluated the safety of our IICP technique and its usefulness for the detection of previously undetected, concomitant remnant PDAC.

PATIENTS AND METHODS

Study population. This study was performed according to the principles of the Declaration of Helsinki. Written informed consent for pancreatic surgery including IICP was obtained from all subjects. We reviewed retrospectively the records of all 93 patients with a preoperative diagnosis of possible IPMN who underwent initial partial pancreatectomy at our institution from April 2007 to March 2012. The indications for operative treatment of IPMN were according to the international consensus guidelines, including all cases of main duct IPMN (MD-IPMN), and branch duct IPMN (BD-IPMN) with abdominal pain, jaundice, pancreatitis, mural nodule, or positive cytology.^{3,4} The study group also included patients with IPMN who did not have any predictors of malignant transformation, but who underwent operations for other reasons, such as PDAC or carcinoma of the duodenal papilla. Among the 73 patients who underwent surgery before December 2010, IICP was performed in 36 patients, at the discretion of the surgeon. Among the 20 patients who underwent surgery from December 2010 to March 2012, IICP was performed in all 12 patients who underwent open

surgery, irrespective of preoperative cytology findings (positive in 7 patients, negative in 5 patients). IICP was not performed in patients who underwent laparoscopic operations. From December 2010, open operations were performed in all patients with positive preoperative cytology, in patients with MD-IPMN who had a mural nodule, and in patients with BD-IPMN who had ≥ 2 of the following: (1) Cyst ≥ 30 mm in diameter, (2) mural nodule, and (3) history of acute pancreatitis.¹⁷ All 48 patients who underwent IICP were enrolled in this study (29 males, 19 females; mean age, 69 years; range, 38–86). Four surgeons performed IICP during the study period.

Preoperative imaging and pancreatic juice collection. All patients underwent preoperative magnetic resonance imaging (MRI)/cholangiopancreatography and computed tomography (CT). IPMN was defined as MD-IPMN or BD-IPMN based on the findings of these examinations.^{3,4} BD-IPMN was defined as IPMN exclusively involving the branch ducts, with grape-like collections of small cysts. MD-IPMN was defined as IPMN with a dilated main pancreatic duct, without grape-like collections. If both grape-like collections and dilation of the main duct were observed, but there were no findings indicating main duct involvement (such mural nodules in the main duct), the dilated duct was considered to be caused by mucin hypersecretion from BD-IPMN and the lesion was classified as BD-IPMN. Mixed-type IPMN was classified as MD-IPMN. Because early stage PDAC cannot easily be detected by CT or MRI, all patients underwent preoperative ERP for pancreatic juice collection for cytologic examination, which was successful in 46 of the 48 patients. Percutaneous, endoscopic, and intraductal ultrasonography were performed when indicated.^{11,17,18}

Cytologic examination. Pancreatic fluid samples were centrifuged at 3,200 rpm for 5 minutes. Sediment smear slides were fixed in 95% ethyl alcohol and polyethylene glycol and stained by the Papanicolaou technique. Two cytologists classified the samples according to the degree of structural and cytologic atypia: Class I, no atypical cells; class II, atypical cells but no evidence of malignancy; class III, atypical cells inconclusive for malignancy (Fig 1, A); class IV, strongly suggestive of malignancy (Fig 1, B); and class V, conclusive for malignancy (Fig 1, C). Class IV and V results were considered positive.

Operative procedures and IICP. The pancreas was cut near the superior mesenteric artery or vein, and planned pancreatoduodenectomy or distal pancreatectomy (DP) was performed.^{19–21} After

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