Patterns of Recurrence After Curative Resection of Pancreatic Cancer, Based on Autopsy Findings

Shoichi Hishinuma, M.D., Yoshiro Ogata, M.D., Moriaki Tomikawa, M.D., Iwao Ozawa, M.D., Kaoru Hirabayashi, M.D., Seiji Igarashi, M.D.

The autopsy findings of patients who died of recurrence after curative resection of pancreatic cancer may afford a reliable guide to increase long-term survival after surgery. Recurrence patterns were analyzed for 27 autopsied patients who had undergone potentially curative resection of pancreatic cancer. The pattern of recurrence was classified as follows: (1) local recurrence, (2) hepatic metastasis, (3) peritoneal dissemination, (4) para-aortic lymph node metastasis, and (5) distant metastasis not including hepatic metastasis, peritoneal dissemination, and para-aortic lymph node metastasis. Of the 27 autopsied patients, recurrence was confirmed for 22 of 24 patients, except for three who died of early postoperative complications. Eighteen (75%) of the 24 patients had local recurrence, 12 (50%) had hepatic metastasis, and 11 (46%) had both. For four patients, local recurrence confirmed by autopsy was undetectable by computed tomography, because the recurrent lesions had infiltrated without forming a tumor mass. Peritoneal dissemination, para-aortic lymph node metastasis, and distant metastasis were found for eight (33%), five (21%), and 18 (75%) of the cases, respectively. Twenty patients died of cancer, but local recurrence was judged to be the direct cause of death of only four. Local recurrence frequently occurs, but is rarely a direct cause of death, and most patients died of metastatic disease. Therefore, treatment that focuses on local control cannot improve the survival of patients with resectable pancreatic cancer, and thus, treatment regimens that are effective against systemic metastasis are needed. (J GASTROINTEST SURG 2006;10:511–518) © 2006 The Society for Surgery of the Alimentary Tract

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Significant advances have been made with regard to the surgical management of pancreatic cancer over the past several decades. As a result, institutes that specialize in surgery to treat pancreatic cancer often report mortality rates of less than 5%. Despite advances in surgical techniques and perioperative care, limited progress has been made in improving the survival rate of patients with resectable pancreatic cancer, and thus, the chances for long-term survival are still poor.[1,2] The 5-year survival rates range from 13% to 25% for patients with pancreatic cancer who undergo potentially curative resection.[2–5] When extended lymph node dissection is performed, particularly in Japan, favorable 5-year survival rates are achievable.[6–9] However, two recent randomized trials could not determine the overall survival advantages for extended lymphadenectomy for patients with pancreatic cancer.[10,11] The value of extended lymph node dissection thus remains to be determined.

The central obstacle to the postsurgical cure of pancreatic cancer is the persistent burden of subclinical locoregional disease that remains even after curative resection is performed. Adjuvant therapy is used to improve survival following curative resection by treating any residual microscopic disease.

Randomized controlled trials involving adjuvant therapy for resectable pancreatic cancer have been limited, but they have guided the current approach to the adjuvant treatment of pancreatic cancer.[12–14] In 1985, the Gastrointestinal Tumor Study Group (GITSG) found a significant survival advantage for adjuvant chemoradiotherapy over surgery alone,[12] and subsequent registered-to-treatment analysis by the same group confirmed the survival benefits of adjuvant chemoradiotherapy.[15] A phase III trial conducted by the European Organization for Research and Treatment of Cancer, however, failed to confirm this benefit.[13] The European Study Group for Pancreatic Cancer recently completed a large scale

randomized controlled trial involving adjuvant che-moradiotherapy or chemotherapy for patients who underwent potentially curative resection of pancre-atic cancer (ESPAC-1 trial).[14] The ESPAC-1 showed a survival advantage for adjuvant chemotherapy, but not one for chemoradiotherapy. The value of adju-vant therapy for resectable pancreatic cancer is in-conclusive, but the results of ESPAC-l could have a major impact on future systems that deliver adju-vant therapy.

With few opportunities for early diagnosis, ag-gressive therapeutic strategies should be established to improve patient outcome based on the assessment of recurrence patterns after curative resection of pancreatic cancer. To increase long-term survival, it is necessary to elucidate the biological properties of the cancer. Autopsy findings of patients who died of recurrence may afford a reliable guide for this purpose. The present study determined the sites of recurrence after curative resection of pancreatic cancer by histopathological examination of autopsied specimens and found that treatment of resectable pancreatic cancer can be refined by increased knowl-edge of the mode of cancer recurrence.

MATERIAL AND METHODS
Patient Characteristics and Operative Procedures

Between September 1986 and August 2004, 85 pa-tients with invasive ductal cancer of the pancreas un-derwent potentially curative resection at the Tochigi Cancer Center Hospital. Sixty-seven of these pa-tients had already died, and 27 patients underwent autopsy 2 to 101 months after surgery. Written in-formed consent to perform an autopsy was obtained from each patient's family. All autopsied patients had undergone pancreatectomy with extended lymph node dissection and en bloc removal of retroperito-neal soft tissues and extrapancreatic nerve plexi, es-pecially around the superior mesenteric, common hepatic, and celiac arteries. Lymph nodes were ex-tensively dissected for group 1 and group 2 lymph nodes as determined by the Classification of Pancre-atic Cancer of the Japan Pancreas Society.[16] Dissec-tion of para-aortic lymph nodes from the level of the celiac artery to the inferior mesenteric artery was also carried out on 21 of the 27 patients. Combined resection of the portal vein in 17 patients was carried out when the tumor was inseparable from the wall of the vein, or a diagnosis of vascular invasion had been made based on preoperative imaging studies. Details of the operative procedures are presented in Table 1.

Adjuvant Therapy

Between September 1986 and August 1994, adjuvant radiotherapy administered at our institute consisted of intraoperative radiotherapy (IORT) and/or postoperative external beam radiotherapy ap-plied to the retroperitoneum (EBRT) for patients 1 to 10 and 25 to 27 as shown in Table 1. IORT was administered just after tumor resection, for which electron beam energies ranging from 6 to 12 MeV were used to deliver 16 to 30 Gy to the treatment field. The treatment field included the tumor bed, roots of the celiac and superior mesenteric arteries, and the 2 cm-long remnant pancreas stump. EBRT was usually started 2 to 3 weeks after surgery, using the same radiation field marked out with surgical clips for IORT at the time of surgery. Patients were treated with 10 MV X-rays using opposing anterior-posterior portals at a dose of 45.0 to 57.6 Gy. Only patient 2, who received EBRT, was con-comitantly given 5-fluorouracil (5-FU).

In 1988 and 1992, Komaki et al.[17,18] observed a decreased incidence of liver metastasis in patients with locally advanced and non metastatic cancer of the pancreas when treated with prophylactic hepatic irradiation (PHI). The decrease as a result of PHI prompted us to use this modality in adjuvant settings combined with pancreatectomy.[19] Since September 1994, PHI has been used as an adjuvant therapy, and 13 patients (patients 11 to 23) in this series re-ceived PHI. In addition, these patients also received IORT (Table 1). PHI was initiated 2 to 4 weeks after surgery using 10 MV X-rays with opposing antero-posterior pair fields. The whole liver was almost equally irradiated with an error of less than 10% of the planned target dose, and the doses varied from 19.8 to 22.0 Gy19. For all patients, 5-FU was con-currently administered by continuous infusion throughout the PHI period.

Stage Classification and Definition of Recurrence Patterns

The sixth edition of the UICC pTNM classifica-tion was used to determine the stage grouping.[20] Patterns of recurrence were classified into five types: (l) local recurrence, (2) hepatic metastasis, (3) perito-neal dissemination, (4) para-aortic lymph node me-tastasis, and (5) distant metastasis not including hepatic metastasis, peritoneal dissemination, and para-aortic lymph node metastasis. Local recurrence was defined as any failure in the retroperitoneum around the superior mesenteric and celiac arteries, including the tumor bed, remnant pancreas, hepatic hilum, or its regional nodes.