Pancreatoduodenectomy for pancreatic head cancer -A 21-year experience-

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Abstract : A total of 24 patients with pancreatoduodenectomy (12 patients) or pylorus-preserving pancreatoduodenectomy (12 patients) for pancreatic head cancer in our department were clinicopathologically reviewed. There were 12 males and 12 females with the mean age of 65 years (range 35-81 years). The presenting manifestation was jaundice in 16 patients, upper abdominal pain in 3, nausea in 3, and general fatigue in 1. The pancreatic remnant was treated by a pancreaticojejunostomy in 18 patients or by a pancreaticogastrostomy in 6 patients. Postoperative complications occured in 16 patients (67.7%). The most common complication was delayed gastric emptying (8 patients). Anastomotic leak developed in 3 patients: pancreaticojejunostomy in 1, pancreaticogastrostomy in 1, and choledochojejunostomy in 1. Operative mortality was 4.2% (1 patient). The final stages were stage III, IV a, and IV b in 11, 7, and 6 patients, respectively. The 1-year, 2-year, and 5-year cumulative postoperative survival was 58.3%, 35.8%, and 0%, respectively. Fifty percent survival was 1.12 year and median survival was 1.17 year (14. 2 months). One patient received external beam radiation therapy (50Gy) for the residual tumor around the portal vein. Fourteen patients underwent postoperative chemotherapy. Adjuvant therapy should be indicated for patients with pancreatic cancer.

Key words : pancreatoduodenectomy, pancreatic head cancer, survival

I . Introduction

In Japan, pancreatic cancer is the fifth leading cause of cancer related mortality in male and the sixth leading cause in female.[1] The disease is often difficult to diagnose, especially in its early stages. Surgical resection remains the only potentially curative treatment, but most patients die within 5 years following resection.[2] In the present article, a total of 24 patients with pancreatoduodenectomy (PD) or pylorus-preserving pancreatoduodenectomy (PPPD) for pancreatic head cancer in our department were clinicopathologically reviewed.

II . Subjects and methods

Data abstracted included demographics, clinical presentation, pathological examination, and postoperative course. Histologic findings were recorded according to the General Rules for the Study of Pancreatic Cancer (JSPC), the 5th edition. Each neoplasm was staged according to the JSPC system.

Follow-up information was obtained by return clinical visits or medical records. Data are given as mean ± standard deviation. The survival time

from the time of surgery was calculated by the Kaplan-Meier method. All analyses were done using the FISHER for windows (NAKAYAMA -Shoten Co., Ltd.). Operative death was defined as death at any time during the first hostipalization, regardless of the length of time.

III. Results

1. Patients

Between June 1984 and May 2004, 24 patients underwent PD or PPPD for a pathologic diagnosis of invasive ductal carcinoma (tubular adenocarcinoma or adenosquamous carcinoma) of the pancreas head at the Shizuoka Red Cross Hospital. There were 12 males and 12 females; the mean age was 65 years (range 35-81 years). The presenting manifestation was jaundice in 16 patients, upper abdominal pain in 3, nausea in 3, and general fatigue in 1.

2. Preoperative Management and Operative Outcome

In 21 out of 24 patients, a preoperative biliary drainage was placed by a transhepatic route (14 patients), by a gallbladder route (5), or endoscopically (2).

The operative procedure was PD in 12 patients and PPPD in 12. We have choiced PPPD in principle since 10 years. The pancreatic remnant was treated by a pancreaticojejunostomy in 18 patients or by a pancreaticogastrostomy in 6 patients. Combined resection of the portal vein was carried out in 5 patients. Lymph node dissection was performed in all patients: D1 (dissection of group 1 lymph nodes alone, 4 patients) and D2 (dissection of group 1 and 2 lymph nodes, 22 patients). The operative time was 455.0 ± 136.0 minutes (range 164-708 minutes) and the intraoperative blood loss was 1264.7 ± 806.5 ml (range 40-3590 ml).

Postoperative complications occured in 16 patients (67.7%). The most common complication was delayed gastric emptying (8 patients). Anastomotic leak developed in 3 patients: pancreaticojejunostomy in 1, pancreaticogastrostomy in 1, and choledochojejunostomy in 1. The other complications were intraabdominal infection in 2 patients, disturbance of consciousness in 2, atelectasis in 1, and wound infection in 1. Operative mortality was 4.2% (1 patient). The patient suffered from leakage of choledochojejunostomy followed by liver abscess, and died of sepsis 131 days after the operation.

3. Macroscopic and Pathological Findings

Macroscopic types were nodular type in 18 patients and invasive type in 6. Tumor size was 2.98 ± 1.11 cm (range 1.3-5.5 cm): 5 TS_1, 15 TS_2, and 4 TS_3.

Results of pathological evaluation showed 14 well-differentiated tubular adenocarcinomas, 8 moderately differentiated tubular adenocarcinomas, 1 poorly differentiated tubular adenocarcinoma, and 1 adenosquamous carcinoma. T Category included 15 t_3 and 9 t_4. Metastatically involved regional lymph nodes were found in 13 patients: 7 n_1, 3 n_2, and 3 n_3. The final stages were stage III, IV a, and IV b in 11, 7, and 6 patients respectively. Macroscopic residual tumor (R2) was found in 6 patients and microscopic tumor (R1) was found in 1.

4. Survival Analysis (figure 1, figure 2)

Follow up was complete to death or to July 2005, thus allowing calculation of actual 5-year survival. All cases were analized irrespective of causes of death. The 1-year, 2-year, and 5-year cumulative postoperative survival was 58.3%, 35.8%, and 0%, respectively. Fifty percent survival was 1.12 year and median survival was 1.17 year (14.2 months). The survival rate in f Stage III was higher than that in f Stage IV, but there was no significant difference between two groups ($p=0.07$ by logrank test, $p=0.08$ by generalized Wilcoxon test). Of the 21 patients who died within 5 years, 18 had recurrences or metastases of the pancreatic cancer: 6 locoregional recurrences, 12 metastases to the liver, 9 metastases to the peritoneum, 10 metastases to the lymph node, 8 metastasis to the lung, and 2 metastases to the bone.

5. Postoperative Therapy

One patient received external beam radiation

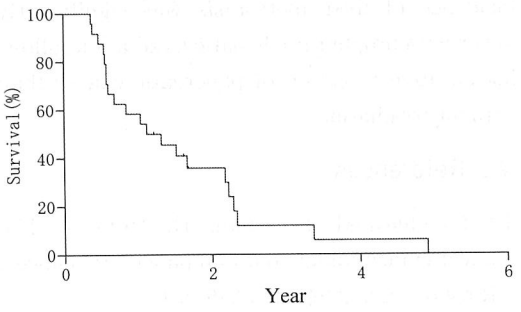

Figure 1. Survival curves of pancreatic cancer of 24 patients

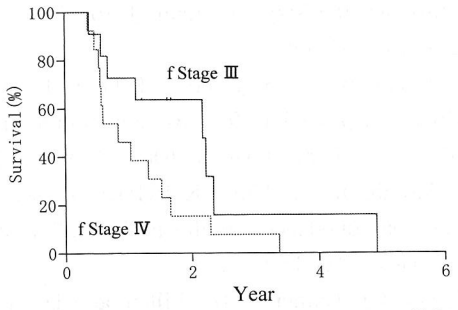

Figure 2. Survival curves of pancreatic cancer (f Stage Ⅲ, Ⅳ)

therapy (50Gy) for the residual tumor around the portal vein. Fourteen patients underwent postoperative chemotherapy when recurrences or metastases were obvious: mitomycin C in 1 patient, fluorouracil (5-FU) in 6, tegafur-uracil in 6, and gemcitabine in 5. In a patient who received gemcitabine, serum carbohydrate antigen level decreased from 4353 U/ml to 974 U/ml, but increased again after that.

Ⅳ. Discussion

PPPD is an alternative to classical PD in patients with pancreatic head cancer. Nagakawa et al.[3] stressed the necessity of PD because cancer-free-margin should be more than 3 cm. On the other hand, Takahashi et al.[4] noted that PPPD could be choiced without metastasis to the suprapyloric lymph nodes and infrapyloric lymph nodes, and without invasion to the bulb. Yeo et al.[5] conducted an randomized controlled trial (RCT) comparing PPPD (n=81) and PD (n=82) in patients with pancreatic head cancer. There was no significant difference in survival between the two groups. At present, there seems to be no conclusive difference between the two procedures. In our institute, PPPD has been ordinarily choiced since 1995.

With regard to lymph node dissection, Nimura et al.[6] has reported a RCT on standard versus extended (regional plus paraaortic) lymph node dissection in PD for pancreatic cancer; extended lymph node dissection did not provide any survival benefit.

There was no consensus on the treatment of locally invasive pancreatic cancer with no distant metastasis. A RCT comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer was conducted in Japan.[7] Operative criteria included pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric artery or the common hepatic artery, and without distant metastasis. Patients assigned to the resection group (n=20) underwent PD or distal pancreatectomy with lymph nodes dissection (D2) and resection of at least a half circle of the plexus of the mesenteric artery. Patients assigned to radiochemotherapy group (n=22) received 200 mg/m^2/day of intravenous 5-fluorouracil and 5040 cGy of radiotherapy without resection. The surgical group had better results than the radiochemotherapy group as mesured by 1-year survival (62% vs 32%, $p=0.05$) and mean survival time (>17 vs 11 months, $p<0.03$). Patients with pancreatic cancer without distant metastasis should be treated by surgical resection.

Despite the decrease of mortality in recent years, PD or PPPD remains a major surgical procedure with high complications. The most common postoperative complication in our institute was delayed gastric emptying (DGE). There was no significant difference in the incidence of DGE between PD and PPPD.[4] One theory regarding the pathogenesis of DGE after PD suggests that gastric atony results from the reduction in circulating levels of motilin, a hormone primarily localized to enterochromaffin cells of the duodenum and proximal small intestine.[8] Yeo et al.[9]

have reported that erythromycin is a safe and inexpensive drug for DGE. We did not use erythromycin. The complication feared most by surgeons after PD or PPPD is an pancreatic leak. We had 2 patients with a minor pancreatic leak which was successfully controled.

Most patients who undergo resection of pancreatic cancer experience recurrcnce; locoregional recurrcnce (23-100%), liver metastasis (39-80%), peritoneum metastasis (17-56%), pulmonary metastasis (1-56%), and bone metastasis (3-24%). 10) Serum level of tumor marker increases before recurrence is obvious on the diagnostic imaging such as computed tomography, magnetic resonance imaging or ultrasonography. Recentry, fluorine-18-2-fluoro-deoxy-D-glucose positron emission tomography has been able to detect recurrences which are not showed by computed tomography or magnetic resonance imaging.[11]

PD for pancreatic cancer is associated with short-term survival. In Japan, 5-year survival and median survival has been reported 13.0% and 12.3 months, respectively.[2] Yeo et al.[5] has stated that 5-year survival in standard resection was 10% and 25% in radical resection. In the present series, 5-year survival and median survival was 0% and 14.2 months, respectively. Adjuvant therapy should be indicated for patients with pancreatic cancer.

The effect of adjuvant treatment on survival in pancreatic cancer is unclear, but some authors has reported a survival benefit of adjuvant chemotherapy or radiotherapy. Yeo et al.[12] demonstrated that adjuvant chemoradiation (5-FU plus external beam radiation to the pancreatic bed) significantly improved survival after PD for pancreatic cancer; median survival with chemoradiation was 19.5 months compared to 13.5 months without therapy. The Europian Study Group for Pancreatic Cancer undertook a large, multicenter trial; the 5-year survival was 21% among patients who received chemotherapy (5-FU plus leucovorin) and 8% among patients who did not receive chemotherapy.[13]

Hishinuma et al.[14] observed that cumulative incidence of liver metastasis was significantly lower with prophyratic hepatic irradiation following curative resection of pancreatic cancer than without irradiation.

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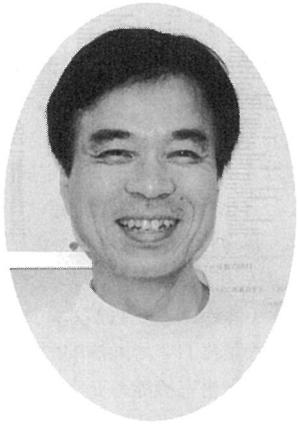

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