



Original article

Optimal duration of the early and late recurrence of pancreatic cancer after pancreatectomy based on the difference in the prognosis



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ABSTRACT

Background: The term “early recurrence” of pancreatic cancer has not been well-defined in most previous studies.

Methods: The clinical records of 86 patients who underwent macroscopic curative pancreatectomy for pancreatic cancer between 2000 and 2009 were retrospectively examined. We divided 55 patients who experienced disease recurrence into two groups, the early and late recurrence groups, using the minimum *p* value approach. The relationships between the interval prior to recurrence and clinical outcomes were investigated.

Results: The cumulative 5-year overall survival rates for all 86 patients were 30.2%. For 55 patients who experienced disease recurrence, the optimal cut-off value for differentiating early (*n* = 37) and late (*n* = 18) recurrence based on the overall survival was 12 months (*p* = 0.0000045). The Cox proportional hazard analysis identified carbohydrate antigen 19-9 > 100 U/ml (*p* = 0.017) and surgical margin (*p* = 0.007) as the independent prognostic factors associated with overall survival. Positive surgical margin (*p* = 0.037) and severe venous invasion (*p* = 0.005) were identified as independent factors associated with early recurrence.

Conclusion: Twelve months after pancreatectomy is the optimal cut-off value for defining early versus late recurrence based on the overall survival. Early recurrence was related to the status of the surgical margin and venous invasion.

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Introduction

Patients with pancreatic carcinoma have a poor prognosis, with a 5-year survival rate of approximately 10–20%, even after curative tumor resection [1–3]. Adjuvant chemotherapy has improved the survival of the patients after surgical resection of pancreatic tumor [4–9]; however, early recurrence of pancreatic cancer frequently occurs after pancreatectomy [10,11]. The time interval between resection for pancreatic cancer and recurrence has been reported to influence the survival time [10], and the early recurrence of

pancreatic cancer is now recognized as an important condition with a poor prognosis [10,11]. However, the term “early recurrence” has never been clearly defined. The period from 6 months to 12 months after pancreatectomy has been used as the early recurrence period in previous reports [10,11]. There is no consensus regarding the meaning of the terms “early recurrence” and “late recurrence” using an evidence-based cut-off value to provide the greatest difference in prognosis between the two groups.

There are several randomized controlled trials that support the use of adjuvant chemotherapy after resection of pancreatic cancer. The European Study Group for Pancreatic Cancer (ESPAC-1) [4] or the Charité Onkologie Clinical-001 (CONKO-001) [12] showed the improved overall survival in the patients with adjuvant chemotherapy. On the other hand, preoperative treatment for pancreatic cancer has been recently attempted [13–15]. Two of the purposes

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for preoperative treatment were to treat micrometastases at an early stage that are likely present at diagnosis and the induction of macroscopic or microscopic downstaging before surgery to increase the R0 resection rate [13,15,16]. It is important to predict the likelihood of early recurrence after pancreatectomy and to assess the risks associated with early recurrence.

The aim of this study was to determine the best cut-off value between the early and late recurrence periods in the patients with pancreatic cancer who underwent pancreatectomy based on the difference in the prognosis for the two groups. In addition, we investigated factors that may contribute to early recurrence, and we evaluated the differences in the prognostic factors for survival between the early and late recurrence groups.

Patients and methods

Patients

A total of 86 patients underwent pancreatectomy procedures for pancreatic cancer between 2000 and 2009 at the Department of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine, and all of these patients were analyzed in this study. Macroscopic curative resection was defined as the absence of apparent tumor residue in the operative field without liver metastasis or macroscopic peritoneal dissemination. All 86 patients had invasive ductal carcinoma of the pancreas. Patients with neuroendocrine cell carcinoma, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (IPMNs) or invasive IPMNs were excluded from this study.

Our principal criteria for performing pancreatectomy included the absence of hepatic metastases, macroscopic peritoneal seeding, bulky lymph node involvement, cancer invasion to the superior mesenteric artery (SMA) or common hepatic artery (CHA) and occlusion of the portal vein. Tumors abutting the entire circumference of the SMA/CHA or the encasement of the SMA/CHA were contraindicated for pancreatectomy. Partial encasement of the portal vein or regional lymphadenopathy was not regarded as contraindications. The removal of the right coeliac ganglion, the first and second portion of the pancreatic nerve plexus and the right side of the plexus around the SMA were principally performed. Fifty-two patients underwent pancreaticoduodenectomy, 28 patients underwent distal pancreatectomy, 1 patient underwent distal pancreatectomy with celiac axis resection and 5 patients underwent total pancreatectomy.

In this study, all patients received D2 lymphadenectomy according to the Japan Pancreas Society (JPS) classification, which was defined as complete removal of the group 1 and group 2 lymph nodes [17]. In the patients with pathologically incomplete resection, we aggressively administered various adjuvant chemotherapeutic regimens during the entire investigation. After results from CONKO-001 trial showed [12], we routinely administered gemcitabine as adjuvant chemotherapy for all patients who underwent pancreatectomy for pancreatic cancer. One patient received gemcitabine plus S-1 as neoadjuvant chemotherapy. Forty-two patients received adjuvant chemotherapy. Twenty-six patients received gemcitabine alone, 6 patients received S-1 alone, 8 patients received gemcitabine plus S-1, 1 patient received 5-fluorouracil plus cisplatin, and 1 patient received tegafur-uracil as adjuvant chemotherapy. One patient received adjuvant radiotherapy. All patients were examined in the outpatient clinic where abdominal ultrasound, computed tomography (CT) and measurement of the levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were performed every three to six months after surgery. The tumors were staged according to the International Union Against Cancer (UICC) and JPS classifications [17,18].

Follow-up

Disease free survival (DFS) was defined as the interval between surgery and the date of diagnosis of the first recurrence or the last follow-up. Overall survival (OS) was defined as the interval between surgery and the date of death caused by pancreatic cancer recurrence or the last follow-up.

Optimal cut-off value between early and late recurrence of pancreatic cancer

Of the 86 patients, 55 patients (64.0%) experienced a recurrence of pancreatic cancer. We divided the 55 patients who experienced a recurrence of pancreatic cancer into two groups: early and late recurrence after pancreatectomy. The minimum *p* value approach, which was performed using the log-rank test for the overall survival, was used to determine the best cut-off with which to divide patients based on their overall survival through 12 months after initial pancreatectomy. This was the longest time to recurrence used in the previous reports [10,11,19–22]. The clinicopathological data were analyzed and compared between patients in the early and late recurrence groups.

Analysis

We performed univariate analyses of the clinical and pathologic factors that were potentially associated with overall survival. Survival was calculated using the Kaplan–Meier method and was compared between groups using the log-rank test. For the purpose of comparing the prognostic value of early recurrence to that of late recurrence, the Cox proportional hazard model was used in analysis of categorical variables influencing overall survival using 86 patients who developed a recurrence of pancreatic cancer. Factors for early recurrence after the initial pancreatectomy for pancreatic cancer were investigated using all 86 patients who underwent pancreatectomy for pancreatic cancer.

All significant factors identified in the univariate analysis were entered into a multivariate regression analysis to identify independent factors. A *p* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 11.5 (SPSS, Chicago, IL).

Results

Optimal cut-off value between early and late recurrence of pancreatic cancer

The cumulative 5-year overall survival (5-year OS) and disease free survival (5-year DFS) rates for all 86 patients together were 30.2% and 13.6%, respectively. Three patients had para-aortic nodal metastasis. Median survival time of patients with para-aortic nodal metastasis is 7.8 months without long survivors. In the 55 patients who experienced a recurrence of pancreatic cancer, the optimal cut-off value between early and late recurrence for dividing patients into two groups based on the greatest difference in overall survival was 12 months ($p = 0.000045$) when using the minimum *p* value approach (Fig. 1). The 37 patients who experienced an initial recurrence of pancreatic cancer within 12 months were defined as the early recurrence group, and the 18 patients who had an initial recurrence after more than 12 months were defined as the late recurrence group. Fig. 2 shows the comparison of the overall survival curves between the early and late recurrence groups. The OS in the late recurrence group was significantly better than that of the early recurrence group. (5-year OS: 9.4% vs. 42.4%, $p = 0.000045$). There was no significant difference in the overall survival between

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