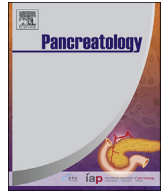




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Is distal pancreatectomy with en-bloc celiac axis resection effective for patients with locally advanced pancreatic ductal adenocarcinoma? -Multicenter surgical group study

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ABSTRACT

Objectives: We retrospectively investigated the operative outcomes of patients who underwent distal pancreatectomy (DP) for invasive pancreatic ductal adenocarcinoma (PDAC) located at the body and tail.

Methods: Data from 395 patients with PDAC who underwent DP with margin-negative resection (R0 or R1) were collected from seven high-volume centers in Japan from 2001 to 2012. Among them, 72 patients underwent DP with en-bloc celiac axis resection (DP-CAR). The remaining 323 patients underwent conventional DP with splenectomy (DP-S). To determine the efficacy of DP-CAR, clinicopathological data were compared between the DP-CAR and the DP-S groups.

Results: The DP-S group consisted mainly of patients with resectable disease (93%), and conversely, all patients in the DP-CAR group had borderline resectable or unresectable disease. The overall morbidity was significantly higher in the DP-CAR group than in the DP-S group (63% vs 47%, respectively; $P = 0.017$). The median survival time (MST) of the DP-CAR group was significantly shorter than that of the DP-S group (17.5 vs 28.6 months, respectively; $P = 0.004$). However, the MST of patients in the DP-CAR group ($n = 61$, 85%) who received adjuvant therapy was significantly longer than that of patients in the DP-S group ($n = 65$, 20%) who underwent R1 resection (21.9 vs 16.7 months, respectively; $P = 0.024$).

Conclusion: DP-CAR followed by adjuvant chemotherapy provided an acceptable overall survival rate in patients with highly advanced PDAC, but should be performed with great caution because of high morbidity. Patients with a high risk of positive surgical margins with DP-S may be candidates for DP-CAR.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading

cause of death in Japan and the fourth most common malignancy in the United States; the 5-year survival rate is approximately 6% in both the United States and Japan [1,2].

More than 75% of cases with PDAC located at the body and tail of the pancreas are considered unresectable at the time of diagnosis [3–5]. The resectability rate of approximately 25% for pancreatic body and tail PDAC is lower than that for pancreatic head PDAC,

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because early tumor spreading to adjacent or distant organs often occurs in the body and tail PDAC [6,7]. The most common reasons for unresectability are the presence of major vascular invasion, liver metastases and peritoneal dissemination at initial presentation.

Distal pancreatectomy with splenectomy (DP-S) is the standard procedure for tumors located at the body and tail of the pancreas. In particular, perineural invasion spreads towards the celiac plexus and ganglions directly or to the nerve plexus surrounding the splenic and common hepatic arteries in PDAC of the pancreatic body. Tumor invasion to the celiac axis (CA) and the superior mesenteric artery (SMA) is defined as unresectable (UR) disease in the National Comprehensive Cancer Network (NCCN) guidelines [8]. Distal pancreatectomy with en-bloc celiac axis resection (DP-CAR) is a surgical procedure combined with en-bloc resection of the CA, common hepatic artery and nerve plexus around the major arteries with preservation of the stomach in its entirety. Surgical indications for DP-CAR are a pancreatic body tumor that invades or abuts the common hepatic artery or celiac artery without invading the root of the gastroduodenal artery and the SMA on preoperative radiological findings or intraoperative findings. Although the procedure adds to the complexity of the surgical technique and has a risk of hepatic and gastric ischemia, it has been shown to be safe, and it is associated with improved overall survival [9–12].

Herein, there is a raised clinical question: which patients are good candidates for this aggressive surgery? In the current study, we investigated the operative outcomes of patients who underwent DP-CAR for advanced PDAC located at the body and tail compared with conventional DP-S. We analyzed the prognostic variables to identify suitable indications for DP-CAR in these patients.

Materials and methods

Patients

This was a retrospective analysis of data collected from seven high-volume centers for pancreatectomy in Japan (Multicenter Study Group of Pancreatobiliary Surgery, established in 2011). All patients with PDAC who underwent margin-negative resection (R0 or R1) in the participating institutions from January 2001 to December 2012 were enrolled in this study. Case report forms (CRFs) contained 58 data fields per patient, including background, perioperative data, pathological diagnosis and survival period, and were designed to maximize accurate data collection with “pop-up boxes” to define complications and grading systems. A total of 13 continuous variables and 45 categorical variables from the database were required for the statistical analyses conducted in this study. The data from 1451 patients who underwent curative resection for pancreatic cancer were registered.

Postoperative pancreatic fistula (POPF) was defined and graded based on the 3-tiered definition proposed by the International Study Group on Pancreatic Fistula [13], and post-operative complications were graded with the Clavien-Dindo classification [14]. Pathological staging of all patients was based on the tumor-node-metastasis (TNM) classification defined by the Union for International Cancer Control (UICC) [15]. Survival time was calculated from the day of surgery through and including the day of death or the day confirmed alive.

Patients with adenosquamous carcinoma, mucinous carcinoma, papillary carcinoma, unidentified few viable cell tumor and undifferentiated carcinoma with poor prognosis were excluded from this study [Fig. 1]. We evaluated a total of 395 patients with PDAC located at the body or tail. DP-S was performed in 323 patients and DP-CAR was performed in 72 patients with locally advanced disease. The primary endpoint was the overall survival (OS) rate, and

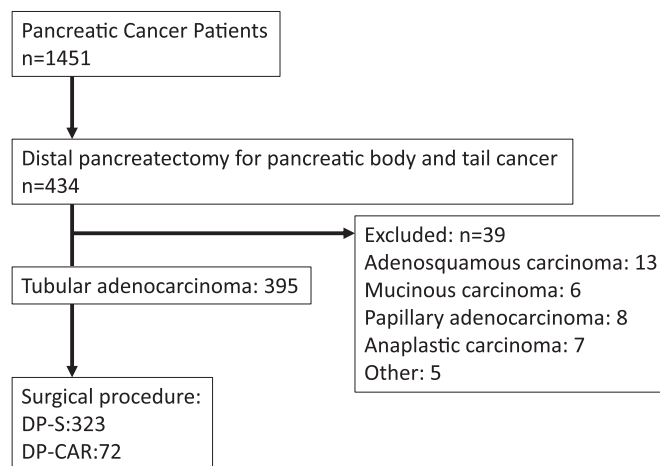


Fig. 1. CONSORT diagram.

Trial profile and patient allocation.

DP-S: Conventional distal pancreatectomy.

DP-CAR: Distal pancreatectomy with en-bloc celiac axis resection.

the secondary endpoint was the post-operative complication rate. Prognostic factors were analyzed for OS, and risk factors for R1 resection and adjuvant chemotherapy were assessed.

Statistical analysis

The database was carefully checked for clerical errors by YM and SS for 1 month before the statistical analyses were initiated in each institution. Missing values were observed in only 0.32% of cases in the database. Data are expressed as median values and ranges.

Statistical analyses were performed with the JMP statistical program version 5.1 (SAS Inc. Cary, NC, USA). The chi-square test or Fisher's exact test was used for comparison of categorical variables when appropriate. Kaplan-Meier survival curves were plotted. Survival analysis was from the day of surgical resection to death or until the end of observation (2013/6/30). We used a Cox proportional-hazards model to estimate the hazard ratios. Multiple logistic regression analysis was also performed to estimate the odds ratio. P values less than 0.05 were considered significant.

Results

Clinical characteristics

Patient characteristics are summarized in Table 1. The median age of the DP-S and DP-CAR groups was 69 and 66 years, respectively. The patients in the DP-CAR group were significantly younger than those in the DP-S group ($P = 0.004$). The resectability status according to the NCCN guideline was significantly different between groups. All patients who underwent DP-CAR were BR or UR, while 93% of the DP-S group was R. Neo-adjuvant therapy was performed in 40 patients (56%) in the DP-CAR group, and 56 patients in the DP-S group (17%; $P < 0.001$). Although the serum level of CA19-9 was not different between groups, the preoperative radiological tumor size in the DP-CAR group was significantly larger than that in the DP group (35 mm vs. 27 mm, respectively; $P < 0.001$). Compared to the DP-S group, the median operative time, blood loss during surgery and PV resection rate of the DP-CAR group were significantly longer and higher. R0 resection was performed in 48 patients in the DP-CAR group (67%), which was significantly lower than in 80% in the DP-S group ($P = 0.019$).

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