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Original article

Prognostic significance of intraoperative peritoneal washing cytology for patients with potentially resectable pancreatic ductal adenocarcinoma

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ABSTRACT

Background: The prognostic significance of intraoperative peritoneal washing cytology (IPWC) in pancreatic ductal adenocarcinoma (PDAC) remains controversial, and the treatment strategy for PDAC patients with positive cytology has not been established.
Objectives: The objective of this study was to evaluate the clinical significance of IPWC in PDAC patients.
Methods: This study included a retrospective cohort of 166 patients with curatively resected PDAC who underwent IPWC.
Results: Overall, 17 patients (10%) had positive cytology (CY+), and 149 (90%) patients were negative (CY−). Tumor location in the pancreatic body and/or tail and pancreatic anterior capsular invasion were independent predictors of a CY+ status (P = 0.012 and 0.041, respectively). The initial recurrence occurred at the peritoneum with a significantly higher frequency in CY+ patients (50%) than in CY− patients (12%) (P = 0.003). The median overall survival (OS) for CY+ patients was 12 months. The OS rates at 1 and 3 years were significantly higher for CY− patients (75.1% and 35.3%, respectively) versus CY+ patients (47.1% and 17.6%, respectively; P = 0.012). However, one CY+ patient survived for 66 months, and another two CY+ patients have survived for more than three years after surgery without evidence of peritoneal recurrence. In the multivariate analysis, the independent predictors of OS were a CY+ status, lymph node metastasis, and adjuvant chemotherapy.
Conclusions: This study demonstrates that positive IPWC predicts early peritoneal recurrence and a poor prognosis for PDAC patients. However, a small but not insignificant subset of CY+ patients with PDAC may avoid peritoneal carcinomatosis.

1. Introduction

Pancreatic carcinoma is the fifth and fourth leading cause of death in Japan and Western countries, respectively, and is associated with an extremely poor prognosis [1,2]. Despite recent advances in radiological imaging modalities, pancreatic cancers are frequently detected late in the disease course. Successful surgical resection offers the only chance for cure in patients with pancreatic cancer, but the 5-year survival rate for patients undergoing complete resection is low (20–25%) even when combined with adjuvant chemotherapy [3–5]. Peritoneal metastasis is one of the most frequent causes of treatment failure following curative resection for pancreatic cancer, with an incidence of 14–33% for patients with recurrence [6,7]. Intraoperative peritoneal washing cytology (IPWC) can detect subclinical peritoneal spread of the disease by directly detecting free cancer cells in the peritoneal cavity. IPWC has been included in the guidelines for tumor staging and is currently a routine procedure for several intra-abdominal malignancies, such as gastric and ovarian cancer [8–10]. However, the prognostic significance of free intra-peritoneal cancer cells in pancreatic ductal adenocarcinoma (PDAC) remains controversial because no randomized controlled trials or prospective follow up studies have investigated this issue. Therefore, the treatment

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strategy for PDAC patients with positive peritoneal cytology has not been established. Several earlier studies demonstrated that PDAC patients with positive peritoneal washing cytology had a poorer prognosis than patients with negative cytology [11–13], whereas conflicting survival data that demonstrated comparable survival of PDAC patients with positive peritoneal washing cytology and patients with negative cytology were presented in other reports [14–16]. However, the number of patients with positive cytology in most previous studies was 20 or less. Recently, Satoi et al. [17] reported a multi-institutional study of 69 PDAC patients with positive peritoneal washing cytology who underwent curative resection. The authors demonstrated that positive peritoneal cytology was an independent prognostic factor for PDAC patients, with a median survival time of 16 months and a 3-year overall survival (OS) rate of 6%. Due to the controversy regarding the prognostic impact of IPWC, the role of peritoneal washing in the staging of pancreatic cancer is still debatable. The current National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma indicate that positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease [18]. In addition, the current American Joint Committee on Cancer (AJCC) staging system for pancreatic cancer classifies positive peritoneal cytology as stage IV disease [8]. However, to date, the Union for International Cancer Control (UICC) TNM classification system and the Japanese General Rules for the Study of Pancreatic Cancer do not include peritoneal cytology for tumor staging [10,19]. The objective of this study was to evaluate the clinical significance of IPWC in patients with potentially resectable PDAC by comparing the IPWC status with the corresponding clinicopathological parameters and clinical outcomes.

2. Patients and methods

2.1. Patients

Between February 1995 and September 2015, a total of 195 patients underwent macroscopically curative resection for PDAC at our institution. This study included a retrospective cohort of 166 patients who underwent IPWC in addition to resection. Patients with visible peritoneal metastases or liver metastases were excluded from this study. This study was approved by the Institutional Review Board. The data obtained from the medical records included clinical characteristics, surgical procedures, IPWC results, histopathological findings, administration of adjuvant chemotherapy, and clinical outcomes. For each patient, the tumor stages were assigned according to the UICC classification system and were based on the surgical and pathological findings. Since 2003, adjuvant chemotherapy was administered to 94 patients (57%) who underwent surgery. The adjuvant chemotherapy regimens were gemcitabine alone (1000 mg/m^2, intravenously administered on days 1, 8, and 15 every 4 weeks [one cycle] for up to six cycles) in 37 patients, S-1 alone (80–120 mg/day according to the body surface area for 28 days followed by a 14 day rest every 6 weeks [one cycle] for up to four cycles) in 54 patients, and gemcitabine plus S-1 [gemcitabine (800 mg/m^2 on day 1) plus S-1 (65 mg/m^2/day on days 1–7) every 2 weeks for six months] in three patients.

2.2. IPWC methods

IPWC was performed according to the Japanese General Rules for the Study of Pancreatic Cancer [19]. Briefly, after opening the abdominal cavity, we introduced 100 ml of physiological saline solution into the Douglas fossa before any manipulation of the tumor and carefully washed the cavity with gentle stirring. The wash fluids were collected from the Douglas fossa using a catheter and a syringe. The fluids were immediately transported to the laboratory and centrifuged at 2500 rpm for 3 min. The cell pellet was aspirated and smeared onto glass slides. Slides were subjected to Giemsa and Papanicolaou staining using a routine procedure. IPWC was graded by experienced cytoscreeners and pathologists. Based on the IPWC results, the patients were classified into the positive cytology group (CY+) or the negative cytology group (CY−). For confirmation, periodic acid–Schiff (PAS) and Alcian blue staining were subsequently performed in all CY+ samples. Patients with equivocal results were classified as CY−.

2.3. Statistical analysis

All data were analyzed using SPSS software, version 23. The chi-squared or Fisher's exact test was used to analyze the categorical variables. The cut-off values for the age and tumor size were defined as 65 years and 40 mm because the mean and median values for each factor were 65.8 and 66.5 years and 43.1 and 38.0 mm, respectively. A multivariate analysis of factors related to CY status was performed using the logistic regression model. Survival curves were constructed according to the Kaplan-Meier method. The log-rank test was used to compare the survival curves. The overall survival (OS) was calculated as the time from the date of surgery to either the date of death or the last follow-up, whichever occurred first. The disease-free survival (DFS) was defined as the time from the date of surgery to the date of recurrence, the last follow-up or the date of death, whichever occurred first. Patients without recurrence at the last follow-up date were censored. Cox proportional hazards models were constructed to evaluate the prognostic significance of CY status with clinical outcomes while adjusting for clinical factors. P values less than 0.05 were considered statistically significant.

3. Results

The clinical characteristics of the 166 patients are outlined in Table 1. Overall, 17 patients (10%) had positive IPWC and were classified into the CY+ group. The remaining 149 patients (90%) included 144 patients with negative cytology and five patients with equivocal results, and these patients were classified into the CY− group. A significant positive correlation was observed between a CY+ status and tumor location in the pancreatic body and/or tail ($P = 0.007$) and the presence of pancreatic anterior capsular invasion ($P = 0.007$) (Table 2). The age, gender, tumor size, serum tumor markers including carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), and duke pancreatic monoclonal antigen type 2 (DUPAN-2), the presence of retroperitoneal invasion, extrapancreatic nerve plexus invasion, lymph node metastasis, UICC tumor stage, and resection status were not associated with the CY status. Tumor location in the pancreatic body and/or tail and the presence of pancreatic anterior capsular invasion were significant factors in the multivariate analysis (OR = 0.184, 95% CI, 0.050–0.687, P = 0.012 and OR = 0.115, 95% CI, 0.015–0.911, P = 0.041, respectively). At a median follow-up of 17.5 months, 116 patients experienced recurrence and 115 patients had died. Among the 116 patients who experienced recurrence, the initial recurrence was mainly observed at the following sites: the liver (n = 55, 47%), a local site (n = 34, 29%), the peritoneum (n = 19, 16%), and the lymph nodes (n = 19, 16%). Only six patients (5%) displayed lung metastasis. The initial recurrence occurred at the peritoneum with a significantly higher frequency in CY+ patients (7 of 14 patients; 50%) than in CY− patients (11 of 93 patients; 12%) (P = 0.003).

The OS rates at 1 and 3 years were significantly higher for patients with a CY− status (75.1% and 35.3%, respectively) than for patients with a CY+ status (47.1% and 17.6%, respectively; P = 0.012)

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