International Journal of Surgery 39 (2017) 169–175

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

The Charlson age comorbidity index predicts prognosis in patients with resected pancreatic cancer

Tomonari Asano, Suguru Yamada*, Tsutomu Fujii, Norimitsu Yabusaki, Goro Nakayama, Hiroyuki Sugimoto, Masahiko Koike, Michitaka Fujiwara, Yasuhiro Kodera

Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan

HIGHLIGHTS

- The overall survival rate was significantly higher in the low-CACI group than in the high-CACI group.
- In the high-CACI group, patients with high RDI for adjuvant chemotherapy had significantly better OS than those with low RDI.
- The CACI was a significant independent predictor of prognosis and compliance for postoperative adjuvant chemotherapy.
- The CACI could be clinically useful for decision-making in the treatment strategy for pancreatic cancer.

ARTICLE INFO

Article history:
Received 22 December 2016
Received in revised form
31 January 2017
Accepted 31 January 2017
Available online 2 February 2017

Keywords:
CACI
Pancreatic cancer
Chemotherapy
RDI

ABSTRACT

Background: The Charlson age comorbidity index (CACI) is a useful measure of comorbidity to standardize the evaluation of surgical patients and has been reported to predict postoperative mortality in various cancers.

Method: A total of 379 patients who underwent R0/R1 resection for pancreatic cancer between 2003 and 2014 were enrolled in this study. According to the CACI, the age-adjusted comorbidity index was calculated by weighting individual comorbidities; CACI<4 was considered the low-CACI group, whereas CACI≥4 was considered the high-CACI group. The correlations between the CACI and clinicopathologic features and survival outcomes were statistically analyzed.

Results: The patients with a high CACI were more likely to be old and had higher CA19-9 levels and lower incidences of portal vein resection and blood transfusion. The rate of patients who received chemotherapy was significantly higher in the low-CACI group than in the high-CACI group (87% vs. 69%, $P < 0.0001$). The overall survival (OS) rate was significantly higher in the low-CACI group than in the high-CACI group ($P = 0.047$). Multivariable analysis showed that a high CACI was a predictor of poor survival ($P = 0.024$). In the high-CACI group, patients with high relative dose intensity (RDI) for postoperative adjuvant chemotherapy had significantly better relapse-free survival (RFS) and OS than those with low RDI (both $P < 0.0001$).

Conclusions: The CACI was a significant independent predictor of prognosis and compliance for postoperative adjuvant chemotherapy in the resected pancreatic cancer.

1. Introduction

The prognosis of patients with pancreatic cancer is extremely poor; specifically, the median survival reported for resected pancreatic cancer ranges from 17 to 27 months, and the 5-year survival is 20% [1–4]. Surgical resection followed by adjuvant chemotherapy is considered the standard treatment for resectable pancreatic cancer, whereas preoperative treatment is usually delivered for borderline resectable cases. Unfortunately, because of the aging population and higher incidence of comorbidities in elderly patients, a higher number of patients in Japan fail to receive standard treatment, and this might affect the outcome of pancreatic cancer patients as a whole [5]. Nevertheless, a previous study demonstrated that advanced age was not an absolute

* Corresponding author. Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
E-mail address: suguru@med.nagoya-u.ac.jp (S. Yamada).

http://dx.doi.org/10.1016/j.ijsu.2017.01.115
1743-9191/

contraindication for surgery in pancreatic cancer patients, and there was no increased mortality after surgery in elderly patients, even in those over 80 years of age [6].

The Charlson age comorbidity index (CACI) is a measure of comorbidity used to standardize the evaluation of surgical patients and has been used to predict the postoperative mortality of patients undergoing surgery in many studies [7–11]. Thus far, CACI has been reported to be an appropriate prognostic factor for hepatocellular carcinoma, breast, gastric and colorectal cancer patients [8,12–14]. However, few studies have examined the use of CACI in pancreatic cancer patients. Additionally, few studies have evaluated therapeutic strategies in elderly patients with several comorbidities.

In the current study, we utilized the CACI and explored the clinical implications of preoperative, operative and postoperative background factors in the patients with resected pancreatic cancer because better outcome prediction will improve preoperative counseling and guidance on the best treatment in an era of multidisciplinary and personalized medicine [7]. Additionally, we investigated whether the CACI could influence the relapse-free survival (RFS) and overall survival (OS), and analyzed the association with compliance of postoperative adjuvant chemotherapy (AC) based on the relative dose intensity (RDI).

2. Patients and methods

2.1. Patients

Between 2003 and 2014, a total of 379 patients with pancreatic cancer underwent resection at the Department of Gastroenterological Surgery, Nagoya University Hospital. These patients include those who had borderline resectable cancer and underwent neoadjuvant chemotherapy. The resected specimens were histologically examined and were confirmed to have carcinoma of the pancreas. Patients with tumors other than pancreatic adenocarcinoma, such as neuroendocrine tumor and intraductal-papillary mucinous neoplasms, and those who underwent R2 resection were excluded from this study. The study was approved by the ethics committee of the hospital.

2.2. Surgical procedure

All 379 patients were considered candidates for curative resection after meticulous preoperative workups. When the patients did not have unresectable lesions due to the presence of macroscopic hepatic metastases or extensive local invasion upon laparotomy, extended radical resection (D2) was performed in all cases [20–22,24]. Reconstruction after pancreatoduodenectomy was performed with modified Child method. Especially, we performed pancreatojejunostomy as derivate procedures in the management of pancreatic stump [23]. The final stage of pancreatic adenocarcinoma was pathologically assessed according to the TNM classification system of malignant tumors published by the International Union Against Cancer [UICC], 7th edition [25].

2.3. Postoperative complications and definitions

Postoperative complications were classified according to the standard morbidity and mortality scoring system described by the Clavien-Dindo (CD) classification [18]. A complication of Grade III or higher was regarded as a clinically significant event. The classification system of the International Study Group of Pancreatic Fistula was used to evaluate the postoperative pancreatic fistula [19]. Postoperative pancreatic fistula of Grade B or more was regarded as a clinically significant event.

2.4. Chemotherapy

In our institution, the neoadjuvant chemotherapy (NAC) was performed for patients who have local advanced pancreatic cancer with an abutting major artery ($n = 41$). The NAC regimens included S-1 with radiation therapy ($n = 39$) or gemcitabine plus S-1 (GS) chemotherapy ($n = 2$).

The patients were eligible for postoperative adjuvant chemotherapy (AC) if they had undergone complete macroscopic resection for pancreatic ductal adenocarcinoma with histological confirmation ($n = 245$). The planned period of AC was 6 months, and administration started immediately after wound healing [26]. The AC regimens included gemcitabine monotherapy ($n = 135$), S-1 monotherapy ($n = 64$) or GS chemotherapy ($n = 46$). The patients received AC with six cycles of gemcitabine every 4 weeks. Each cycle consisted of three weekly infusions of 1000 mg/m^2 gemcitabine given by intravenous infusion during a 30-min period, followed by a 1-week pause. The S-1 regimen was 80–120 mg, according to body surface, twice per day for 4 weeks and then repeated every 6 weeks for 4 courses. In the GS regimen, patients received gemcitabine (800 mg/m^2, day 1) plus S-1 (65 mg/m^2/day, days 1–7) every 2 weeks.

The RDI was calculated as the quota of real dose intensity administered to the scheduled dose intensity according to the chemotherapeutic protocol.

2.5. Preoperative comorbidity and the Charlson age comorbidity index (CACI)

Information regarding the comorbidities of the enrolled patients was retrospectively retrieved from the patient charts using manual reviews of the clinical history.

The Charlson Age Comorbidity Index (CACI) was calculated by adding the comorbidity score and the age-adjusted comorbidity index. The comorbidity score was calculated at the time of pancreatic cancer diagnosis based on the clinical history (Supplementary Fig. 1) [15–17]. The age-adjusted comorbidity index was calculated by weighting individual comorbidities and adding 1 point per decade to ages >40 years (i.e., 50 years, 1; 60 years, 2; and 70 years, 3). According to this approach, a patient 40 years of age would be assumed to have no risk of comorbid death attributable to age and a patient with a comorbidity index score of 0 would have no risk attributable to pre-existing comorbid disease [17].

In the current study, the cut-off value for the CACI (<4 or ≥4) was arbitrarily determined based on the median and average CACI values of the study participants.

2.6. Statistical analysis

The statistical analysis was performed using Student's *t*-test, the x^2 test, or Fisher's exact probability test as appropriate. Patient survival was determined from the time of surgery to the time of death or most recent follow-up. The median follow-up periods were 14.9 months (range 0.43–117 months). Postoperative survival was calculated using the Kaplan-Meier method, and differences in the survival curves were compared with the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses. All analyses were performed with JMP ver.11 software (SAS Institute Inc., Cary, NC, USA). Values of $P < 0.05$ were considered statistically significant.