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Long-term outcomes in elderly patients with resectable large hepatocellular carcinoma undergoing hepatectomy

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ABSTRACT

Background: In contrast to the feasibility of hepatectomy for resectable large hepatocellular carcinoma (HCC, > 5 cm) in the younger patients, the concerns of benefits for the elderly patients remain in practice. This study aimed to evaluate the long-term outcomes and safety after hepatectomy in elderly patients with resectable large HCC compared with younger patients.

Methods: Between 2003 and 2014, a total of 2211 HCC patients were reviewed using a prospective database and 257 patients with resectable large HCC undergoing hepatectomy were included: 79 elderly patients with age ≥70 years and 178 younger patients with age < 70 years. The last follow-up was assessed in December 2017. The complications, long-term outcomes and risk factors of disease-free and overall survival were analysed.

Results: The 1-, 3-, 5- and 7-year overall survival rates in the elderly and younger groups were 76%, 55%, 48%, and 42% and 79%, 57%, 51%, and 49%, respectively (P = 0.319). The 1-, 3-, 5-, and 7-year disease-free survival rates in the elderly and younger groups were 60%, 40%, 38%, and 27% and 54%, 36%, 32%, and 32%, respectively (P = 0.633). The analysis of post-operative outcomes of interest, including hospital stay and hospital death and hepatectomy-related complications in both groups revealed no significant difference. Serum albumin and AJCC TNM stage were independent risk factors for survival. Serum alpha-fetoprotein, tumour number and AJCC TNM stage predicted HCC recurrence.

Conclusions: Our results suggested that hepatectomy can achieve comparable long-term outcomes in the selected younger and elderly patients with resectable large HCC.

1. Introduction

Hepatocellular carcinoma (HCC) remains the important health issue in the men and women worldwide, especially in Taiwan [1,2]. The etiologies of HCC include hepatitis B/C virus infection, alcoholic liver disease, nonalcoholic steatohepatitis and cirrhosis [3]. Surgical treatment is still the main modality of curative treatment for HCC, although other safe and efficient therapies, including radiofrequency ablation (RFA), percutaneous ethanol injection, and transarterial chemoembolization (TACE), have been advanced and applied [4,5]. To date, several staging systems, containing clinicopathological parameters, have been used to predict the prognosis of HCC [6]. Among these, the Barcelona Clinic Liver Cancer (BCLC) classification is frequently used as a guideline for treatment options in HCC patients [7,8]. Patients with single nodule (> 5 cm) or multinodular tumors, Child-Pugh A-B and Eastern Cooperative Oncology Group (ECOG) performance status 0 are classified as BCLC stage B (intermediate-stage) and the treatment of TACE is recommended [9]. However, some cohort studies recently showed that hepatectomy resulted in better overall survival and recurrence-free survival rate for large HCC (> 5 cm), compared to TACE [10–12]. As to the elderly (age ≥70 years), hepatectomy has been accepted as a curative method for selected patients with small HCCs, suggesting that age is not a determining factor for hepatectomy [13–15]. Moreover, one study showed that repeat hepatectomy may be warranted for selected elderly patients with recurrent HCC [16,17].

In clinical practice, hepatectomy is being gradually accepted as a first-line treatment for younger patients with resectable large HCC [18,19]. The efficacy of hepatectomy for the elderly patient with

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resectable large HCC is unclear. This study aimed to evaluate the long-term outcomes and safety after hepatectomy between the elderly and younger patients with resectable large HCC. It is the largest population study to focus on elderly patient with resectable large HCC after 21th century.

2. Materials and methods

2.1. Patients

Approval for this study was obtained from institutional review board of Tri-Service General Hospital (No. TSGH-C102-145). This cohort study was conducted as a retrospective analysis from the database of the cancer board. Between 2003 and 2014, a total of 2211 patients with an established diagnosis of HCC at our hospital were reviewed. All patients were evaluated by surgeons and hepatologists to determine the feasible operation, based on technical resectability of tumor, liver function and patient's general condition. Informed consents for the treatment were obtained from all patients. In the period of this study, tumor size and number were not considered as absolute criteria for surgery. The inclusion criteria for this study were tumor size > 5 cm, technically resectable tumor, and patients in good general condition (the American Society of Anesthesiologists (ASA)) class 1 or 2. The exclusion criteria were Child-Pugh score of ≥8, extra-hepatic metastases, preoperative treatment (TACE, RFA or others) and uncontrolled comorbidities. The remaining 257 patients who met the criteria were collected and divided into the elderly group (≥70 years, n = 79) and the younger group (< 70 years, n = 178). The definition of elderly group is age of 70 or over according to previous published studies [20,21].

The diagnosis of all HCC was according to pathological findings or European Association for the Study of the Liver consensus conference guidelines: (1) concordant results of 2 radiology techniques with contrast enhancement in the arterial phase and venous washout features or (2) typical image finding in 1 image combined with an α-fetoprotein (AFP) level > 200 ng/ml [22].

2.2. Hepatic resection

The indication and extent of HR for large HCC (> 5 cm) patients was based on tumor location; the number of tumors and Makuuchi's criteria, which consist of ascites; total serum bilirubin; and the indocyanine green retention rate at 15 min [23]. The residual liver volume was estimated from a preoperative volumetric computed tomography scan. Hepatectomy was not performed in patients with remnant volume less than 30% of total liver volume excluding tumor mass [24]. Surgery was carried out under general anaesthesia via midline, reversed L-shaped, or subcostal incision with midline extension laparotomy. Intra-operative ultrasound was routinely used. Hepatectomy with/without the Pringle's manoeuvre (20 min and a 5-min clamp-free interval) was performed [25]. One or two 10 Fr. Jackson–Pratt drains were placed after surgery.

2.3. Assessment and follow-up

All patients were evaluated with a history and physical examination, blood laboratory tests, imaging studies (ultrasound, CT, magnetic resonance imaging scan, and/or angiography), and even biopsy for pathological diagnosis according to the European Association for the Study of the Liver guidelines. After hepatectomy, patients were assessed regularly for recurrence by serum AFP level (every 1–2 month) and by ultrasonography, dynamic CT, or magnetic resonance imaging scan (every 3 months). Clinicopathological characteristics, type of hepatectomy, intraoperative and postoperative data were recorded. Suspicious intrahepatic recurrence was confirmed by hepatic angiography. In equivocal situations, image-guided fine-needle aspiration cytology was performed for definite diagnosis. If tumor recurrence was found at follow-up examinations, patients were treated by TACE, RFA, hepatectomy or others (radiotherapy, chemotherapy and target therapy). All patients were followed until December 31, 2017, death, or loss to follow-up. The presence or absence of preoperative comorbidities except HCC was recorded and the severity of comorbidity was assessed using the Charlson comorbidity index [26]. Hospital mortality was defined as death during the postoperative hospital stay. Hepatectomy-related complications are classified according to Clavien–Dindo system [27]. Tumor size was defined as the maximal diameter of the single tumor or, in cases of multiple tumors, the maximal diameter of the largest one.

2.4. Statistical analysis

Statistical analyses of the data were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were expressed as the number (percentage) of events. The Manne-Whitney *U* test and the chi-square test were performed to compare continuous variables and categorical variables between the 2 groups. Overall survival (OS) was defined as the time between the date of hepatectomy and the date of death or the date of the last follow-up for surviving patients. Disease-free survival (DFS) was defined as the time between the date of hepatectomy and the date of recurrence or the date of the last follow-up/the date of death for patients. The OS and DFS rate were estimated using the Kaplan–Meier method and were compared using the log-rank test. The univariate analysis of variables on OS and DFS of HCC was done with Cox's proportional hazard regression model and was compared with the log-rank test. Multivariate analysis of independent factors for OS and recurrence of HCC was carried out with Cox's regression model.

3. Results

3.1. Clinicopathological characteristics of patients

The baseline characteristics of the included 257 patients aged 70 years or older (the elderly group; n = 79) or aged less than 70 years (the younger group; n = 178) are listed in Table 1. The elderly group consisted of 62 men and 17 women, with a mean age of 77.7 years (SD, 5.9 years). The younger group included 146 men and 32 women, with a mean age of 51.3 years (SD, 11.4 years). The demographic and pathological variables, including age, sex, viral hepatitis B or C, platelet count, albumin, total bilirubin levels, and ALT levels, serum AFP, tumor size, tumor number, microvascular invasion, grade of differentiation, Okuda stage and AJCC TNM stage were not significantly different between the two groups. The Charlson comorbidity index sores were not significant different between the elderly and younger groups (3.45 ± 0.65 vs 3.29 ± 0.62, p = 0.091).

The operative and postoperative characteristics of the groups are summarized in Table 2. The percentage of major hepatectomy (> 2 segmentectomy) was not significantly different between the elderly and younger groups (57.0% vs 65.25%, P = 0.213). Other variables, including Pringle maneuver, anterior approach technique, operative time, blood loss and blood transfusion were not significantly different in both groups. Postoperative outcomes, including hospital stay and hospital death were not significantly difference between the elderly and younger groups (11.0 ± 4.7 days vs 11.1 ± 5.4 days, P = 0.924 and 3.8% vs 2.8%, P = 0.704, respectively).

3.2. Detailed hepatectomy-related complications

Surgical complications are not uncommon for patients who underwent liver resection, particularly in large HCC cases. In this study, hepatectomy-related complications classified as Clavien–Dindo grade 3 or