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Liver resection for recurrent hepatocellular carcinoma to improve survivability: a proposal of indication criteria

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ABSTRACT

Background. Despite curative resection of hepatocellular carcinoma, patients have a high probability of recurrence. We examined indications for liver resection in cases of recurrent hepatocellular carcinoma.
Methods. Patients undergoing a second liver resection ($n = 210$) or treatment by transcatheter arterial chemoembolization ($n = 184$) for recurrent hepatocellular carcinoma of up to 3 lesions were included. We developed a prediction score based on prognostic factors and compared survival according to this prediction score.
Results. The prediction score was based on 3 independent variables identified by survival analysis in 210 patients undergoing a second liver resection and included age ≥ 75 years, tumor size ≥ 3.0 cm, and multiple tumors. Each patient was assigned a total score. Median overall survival in patients undergoing a second liver resection with scores of 0, 1, and 2/3 were 7.9 years (95% confidence interval, 5.6 – NA), 4.5 years (3.8 – 6.2), and 2.6 years (2.1 – 5.3), respectively ($P < 0.001$). Among patients with a score of 0, the survival in patients undergoing liver resection was greater than survival in those undergoing transcatheter arterial chemoembolization (median 7.9 [95% confidence interval, 5.6 – NA] years versus 3.1 [2.1 – 3.7] years, $P < 0.001$), and resection was an independent factor for survival. In contrast, survival did not differ in patients with scores 2/3 (2.6 years [95% confidence interval, 1.9 – 5.3] versus 2.3 years [1.6 – 2.8], $P = 0.176$).
Conclusion. Liver resection is recommended as first-line therapy for recurrent hepatocellular carcinoma in patients with a score of 0, while those with score 2/3 should be considered candidates for transcatheter arterial chemoembolization.

Introduction

Despite the advances in diagnosis and treatments for hepatocellular carcinoma (HCC), patients have a high probability of recurrence even after curative resection of early stage HCC.[1] Previously, we reported that the cumulative recurrence rates at 5 years after liver resection were 70% in classic HCC[2] and 56%–62% in early HCC.[1,3] Most patients undergoing curative treatments have the potential for tumor recurrence because of intrahepatic metastasis or multicentric hepatocarcinogenesis; therefore, the next-generation managements of HCC should focus on treatment strategies for recurrent HCC.

For recurrent HCC, a second liver resection has become a *safe* procedure regardless of adhesions and anatomic changes in the liver after the initial resection. Furthermore, a second liver resection has contributed to the improvement of survival with reported survival rates at 5 years after a second liver resection ranging 56%–67%.[4-6] In addition, 3 or more liver resections are now feasible[7-9] with the development of bioresorbable membranes[10] and 3-D computed tomography (CT).[11]

In addition to liver resection, survival outcomes after various treatments, including transcatheter arterial chemoembolization (TACE),[12,13] radiofrequency ablation,[14-16] and salvage transplantation, have been reported.[17-19] But the treatment of such nodules remains controversial; thus, treatment criteria based on liver function and tumor status should be established.

To establish a potential treatment strategy for recurrent HCC, we developed a prediction score after curative resection based on prognostic factors measured after liver resection for recurrent HCC. Subsequently, we compared survival according to the prediction score to identify suitable candidates for a second liver resection.

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Methods

Patients

The study population consisted of patients undergoing liver resection for HCC from the years 2000 to 2015 at the Nihon University Itabashi Hospital, Tokyo, Japan. All patients were observed closely during each outpatient visit. Clinical characteristics and outcomes were compared between patients undergoing liver resection and those undergoing TACE for recurrent HCC.

Inclusion and exclusion criteria

Patients with intrahepatic recurrence of HCC with up to 3 lesions during the follow-up period were included in this study. Patients with extrahepatic recurrence, those with >3 recurrent tumors, and those undergoing treatments other than liver resection or TACE for recurrent HCC were excluded from the study.

Indications for liver resection

The indications for liver resection and the operative procedure were determined by assessing the liver functional reserve according to the Guidelines on Liver Cancer Examination and Treatment in Japan[20] and the criteria of Makuuchi et al for liver resection,[21] respectively. Briefly, liver resection was contraindicated in patients who had refractory ascites or hepatic encephalopathy. Patients with up to 3 lesions were candidates for liver resection. Conversely, the extent of liver resection was determined on the basis of the serum total bilirubin level and by the value of the indocyanine green clearance rate at 15 min (ICGR15). The anatomic resection of Couinaud's segment was considered the first-line operative treatment for HCC. If the patients were not candidates for liver resection according to these criteria, they underwent TACE for intrahepatic tumors and chemotherapy for extrahepatic lesions.

To assess the existence of esophageal varices and gastrointestinal ulceration, gastrointestinal endoscopy was performed preoperatively for all candidates eligible for liver resection. If the patients had high-risk esophageal varices (huge F3 varices or intermediate F2 varices positive for red color signs), they were treated prophylactically using esophageal variceal ligation.[22]

Operative procedures

Open liver resection was performed in all patients according to criteria based on liver function. Transection of the liver was performed under ultrasonographic guidance, using the clamp-crushing method with the inflow-blood–occlusion technique.[23] Closed irrigation drains were placed near each cut surface of the liver.[24] Curative resection was defined as the complete removal of all recognizable HCC diagnosed preoperatively or intraoperatively with tumor-free surgical margins. Postoperative complications were stratified according to the Clavien-Dindo classification,[25] which defines morbidities as complications with a score of ≥IIIa. Complications specific to liver resection were defined as described previously.[26]

Follow-up after operation

All patients were followed up for postoperative recurrence as described previously.[3] Briefly, tumor marker levels were measured and imaging studies, including CT and ultrasonography, were performed every 3 months in all patients. Recurrence was diagnosed by dynamic CT or gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced magnetic resonance imaging (MRI). The date of recurrence was defined as the date of examination when recurrence of the HCC was detected. In patients with recurrent HCC, the recurrence-free period was defined as the time between the date of operation and recurrence. Recurrent HCC was managed aggressively by repeated liver resection, TACE, and chemotherapy according to the HCC status and liver function at the time of recurrence.

Treatments for recurrent HCC

A second liver resection was the first-choice treatment for recurrent HCC, if the operation was feasible on the basis of liver function and tumor status, which were evaluated using the same criteria as those at the time of initial operation.[4,21] TACE was repeated if a second resection was contraindicated because of the following reasons: poor liver function, patient disapproval or refusal of another operation, and severe complications at the initial resection.

Prediction score

Prediction scores for survival after treatment consisted of clinicopathologic factors that were associated with overall survival on multivariate analyses and were defined as follows: one point was added for each of the independent risk factors for overall survival identified by the Cox proportional hazards regression model, and the scores for variables related to overall survival were calculated. Each patient was then assigned a total score.

Statistical analysis

Data collected from each group were analyzed statistically with Fisher exact test and the Wilcoxon rank sum test. Survival curves were generated using the Kaplan-Meier product-limit method and compared by the log-rank test. Prognostic factors for overall survival were identified with the Cox proportional hazards regression model. A P value < 0.10 was set as the cut-off value for elimination. The following 19 variables, considered potential confounders, were examined: tumor size (≥3.0 versus <3.0 cm), tumor number, grade of differentiation, tumor thrombus of the portal vein and hepatic vein, liver cirrhosis at first operation, age (≥75 versus <75 years), sex, disease-free interval (≥2.0 versus <2.0 years), esophageal varices, diabetes mellitus, positive for hepatitis B virus and C virus, serum alpha-fetoprotein level (≥100 versus <100 ng/mL), serum des-gamma carboxyprothrombin level (≥100 versus <100 ng/mL), ICGR15 (≥15% versus <15%), Child-Pugh classification (A versus B), and tumor size and number of tumors at second operation.

Results

Patients

Of the 1,052 patients who underwent curative liver resection for HCC, 673 (63.9%) were diagnosed as having a recurrent HCC. Among these patients, 216 (20.5%) and 311 (29.5%) underwent second liver resection and TACE for recurrent tumors, respectively. After excluding patients based on the criteria described, 210 (19.9%) patients undergoing liver resection and 184 (17.4%) undergoing TACE were included in the study (Fig 1). Among the study participants, when comparing the second operation group with the TACE group, the median age of 70 years (range, 42 – 84) in the operation group was somewhat less than the 73 years (range, 36 – 87) in the TACE group ($P = 0.003$), the incidence of esophageal varices was greater (36.9% versus 26.6%), and the disease-free interval was also somewhat greater at 1.9 years ([range, 0.2 – 7.8] versus 1.5 years [range, 0.1 – 6.1]; $P = 0.002$) (Table 1).

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