Pathologic response to preoperative transarterial chemoembolization for resectable hepatocellular carcinoma may not predict recurrence after liver resection

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BACKGROUND: Pathologic response (PR) predicts survival after preoperative chemotherapy and resection of a malignancy. Occasionally, transarterial chemoembolization (TACE) may be selected for preoperative management of resectable hepatocellular carcinoma (HCC). This study investigated whether PR to preoperative TACE can predict recurrence after resection for resectable HCC.

METHODS: We conducted analysis of 106 HCC patients who underwent TACE followed by liver resection with a curative intent. The PR was evaluated as the mean percentage of nonviable tumor area within each tumor. We divided the patients into three groups according to response rate: complete PR (CPR), major response (MJR: PR≥50%) and minor response (MNR: PR<50%). The primary endpoint was disease-free survival, and the secondary endpoints were predicting factors for tumor recurrence and MJR+CPR.

RESULTS: Among the 121 TACE patients, PR could be measured in 106 (87.6%). The mean interval between TACE and liver resection was 33.1 days. The 5-year disease-free survival rates by PR status were as follows: 40.6% CPR, 43.7% MJR, and 49.0% MNR (P=0.815). There were also no significant differences in overall survival between the three groups. Multivariate analyses revealed that microvascular invasion and capsular invasion (hazard ratio [HR]=11.224, P=0.002 and HR=2.220, P=0.043) were independent predictors of disease-free survival. Multivariate analysis of the predictors of above 50% PR revealed that only hepatitis B was an independent factor.

CONCLUSION: These data could reflect that the PR after TACE for resectable HCC may not be useful for predicting recurrence of HCC after resection.

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KEY WORDS: pathologic response; transarterial chemoembolization; hepatocellular carcinoma; neoplasm recurrence

Introduction

Apart from liver transplantation, liver resection is the clear mainstay of curative treatment for hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE) was introduced during the late 1970s as a palliative treatment for patients with unresectable HCC. In some centers, a single session of TACE is routinely performed before liver resection to ensure that additional small satellite HCC nodules are detected on a computed tomography (CT) scan performed 2-3 weeks later.[1,2] Today, TACE is commonly used for patients who are awaiting liver transplantation to prevent wait-list dropout and to improve post-transplant survival.[3] The induction of tumor necrosis is a direct effect of preoperative TACE and may be the intent of preoperative TACE. For the purpose of achieving complete tumor necrosis, preoperative TACE could be performed frequently.

A recent systematic review[4] demonstrated that using TACE preoperatively as a neoadjuvant treatment in resectable HCC is a safe and efficacious procedure with high rates of pathologic responses (PRs). However, it does not appear to improve disease-free survival (DFS). Pathologic tumor response to chemotherapy has recently

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been recognized as an important prognostic factor in patients who have been treated with preoperative chemotherapy for other gastrointestinal tract cancers such as gastric and colorectal cancer.[5-7] PR predicts survival after preoperative chemotherapy and resection of some malignancies.[8-10]

Regarding the relationship between tumor necrosis and survival, Adachi et al[11] reported that preoperative TACE resulted in better DFS rates if it produced complete tumor necrosis. In contrast, a number of reports have revealed that the direct effects of TACE, such as complete tumor necrosis, did not influence the recurrence rate after curative resection.[1, 12, 13] In the setting of resectable HCC, this area of study has not been reported. Herein, we investigated whether PR to preoperative TACE can predict recurrence after resection for resectable HCC.

Methods

Study population

Approval for this study was obtained from the institutional review board. Between July 2000 and March 2013, 137 patients with HCC underwent initial liver resection with curative intent at the Department of Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea. In the 137 patients, 121 underwent preoperative selective TACE. PR could be measured in 106 of those 121 patients from their pathology reports. Eventually, the 106 patients were enrolled in this investigation and divided into three groups according to response rate: complete PR (CPR), major response (MJR: PR≥50%) and minor response (MNR: PR<50%).

Our selection criterion for liver resection for HCC patients was well-compensated chronic liver disease (Child-Pugh class A/B) without signs of severe portal hypertension (esophageal varices less than G2) and with a platelet count of at least 50×10^9/L. Resection volume limitation was decided based on the patient's indocyanine green retention rate at 15 minutes (ICG-R15). This study was retrospective, and the decision to apply TACE before surgical resection was not controlled intentionally by the authors. Hepatologists in our institution preferred to perform this procedure, and surgeons did not.

Selective TACE procedure

After catheterization of the femoral artery, an aortography showed the celiac trunk and mesenteric arteries. The feeding arteries to the lesions were catheterized as selectively as possible, followed by embolization. A mixture of lipiodol (2 mL) and adriamycin (10 mg) was injected after complete emulsification into the supplying artery until the flow stopped. The dosage was adjusted to the physical constitution of the patient's liver function and tumor size. The amount of adriamycin was increased to a maximum of 50 mg in large tumors.

Follow-up and definition of recurrence

After discharge, all patients were followed up regularly in the outpatient clinic and monitored for recurrence by a standard protocol including serum alpha-fetoprotein (AFP) level monthly for 6 months postoperation and received ultrasound or contrast CT scan every 3-6 months for 5 years. Chest X-ray was also performed at each visit. Recurrence was diagnosed if there was radiological evidence of recurrence with or without an elevated level of AFP supplemented with tissue biopsy if necessary.

Pathologic examination

Tumor location, greatest dimension, type of margins, histological degree of differentiation defined according to the Edmondson and Steiner classification, tumor necrosis, satellite lesions, and macroscopic or microscopic vascular invasion were reported for each single nodule of HCC.[14, 15] In this study, tumor necrosis was considered complete when the pathologists reported 100%. When the necrosis was above 50% or under 50% in the whole tumor area, MJR or MNR was diagnosed, respectively. Tumor size was reported according to the largest size of the nodule, regardless of the presence of viable tumor or necrotic tissue. When patients had multiple lesions, only the worst tumor characteristics were reported for each patient.

Study endpoints

The primary endpoint was DFS after resection of HCC, and the secondary endpoints were risk factors for tumor recurrence and predicting factors for above 50% response rate of TACE.

Overall survival was defined as the time interval between liver resection and death or the date of the last follow-up. To assess DFS, patients were censored at either the time of recurrence or death. Patients without evidence of recurrence were censored at the time of last follow-up or death.

Statistical analysis

One-way analysis of variance was performed to compare continuous variables. Categorical variables were compared by using the Chi-square test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method and compared between groups with the log-rank test. Univariate analysis was performed to identify factors that could influence recurrence. Logistic regression analysis was performed to investigate the