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Hepatectomy versus stereotactic body radiotherapy for primary early hepatocellular carcinoma: A propensity-matched analysis in a single institution☆

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ABSTRACT

Objective: To evaluate the efficacy of both surgical resection and stereotactic body radiotherapy for small hepatocellular carcinoma.
Background: Although the number of stereotactic body radiotherapies being performed for hepatocellular carcinoma has gradually increased, data comparing surgical resection and stereotactic body radiotherapy are limited.
Methods: Between 2008 and 2015, a total of 281 patients with 1 to 3 small hepatocellular carcinoma tumors ($\leq$3 cm in diameter), treated initially with curative intent (surgical resection, 254; stereotactic body radiotherapy, 27), were retrospectively analyzed. Overall survival and disease-free survival were compared in a propensity score matching analysis.
Results: Patients in the surgical resection group tended to be younger, had more tumors, and had better hepatic function than those in the stereotactic body radiotherapy group ($P < .05$). The percent recurrence of the same sub-segment in the stereotactic body radiotherapy group was significantly higher than that in the surgical resection group ($P = .0034$). Propensity score analysis revealed that 54 patients with surgical resection and 27 with stereotactic body radiotherapy had the same baseline characteristics. The 5-year overall survival and disease-free survival rates for the surgical resection and stereotactic body radiotherapy groups were 75.2% vs 47.8% ($P = .0149$) and 33.8% vs 16.4% ($P = .0512$), respectively. Multivariate analysis showed that surgical resection was a significant favorable factor for overall survival and disease-free survival of patients with one to three small hepatocellular carcinomas.
Conclusion: Surgical resection provided better long-term overall survival and disease-free survival in patients with small hepatocellular carcinoma tumors. However, stereotactic body radiotherapy may be an effective alternative treatment for inoperable patients with early hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is among the most common malignant diseases and the second leading cause of cancer-related deaths worldwide.[1] In the Barcelona Clinic Liver Cancer guidelines for HCC treatment, surgical resection (RES) and liver transplantation are considered the first-line treatments for early stage HCC patients.[2] In addition, local ablation with radiofrequency (RFA) or percutaneous ethanol injection (PEI) is considered the standard of care for patients not eligible for surgery. Several previous studies reported that the 5-year overall survival (OS) for patients who underwent resection was 27% to 70%, while the 5-year OS of those who underwent transplantation was 44 to 78%.[3–5] In other studies, it was found that the 5-year OS after RFA and PEI was 40%

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to 70%[6,7] and 47% to 53%,[8,9] respectively. Radiotherapy is currently being explored as a treatment modality in the management of HCC; however, no evidence supports its therapeutic benefit for HCC.[2]

Several studies on liver stereotactic body radiotherapy (SBRT) for HCC have reported a good 3-year local control rate (91.0%–96.3%) with a low risk of severe toxicity.[10,11] Therefore, SBRT has become a treatment option for HCC patients who are not eligible for surgery, local ablation, or liver transplantation. Comparison of treatment outcomes between RFA and SBRT was conducted by Wahl et al,[12] who showed that both procedures provide excellent local control for small HCC with minimal overall toxicity, resulting in 1- and 2-year local progression-free survival rates of 83.6% and 80.2% for RFA and 97.4% and 83.8% for SBRT. Recently, Su et al reported that stereotactic ablative radiotherapy (SABR) had an advantage over resection as SABR is less invasive for patients with small primary HCC.[13] Sapisochin et al reported the safety and efficacy of SBRT compared with TACE and RFA, as a bridge to liver transplantation, using an intention-to-treat analysis.[14] They found that SBRT might be safely utilized as a bridge for liver transplant patients with HCC as an alternative to conventional bridging therapies. Although the number of radiotherapy procedures performed for HCC is gradually increasing, comparison data for hepatectomy and radiotherapy are currently inadequate to draw conclusions.

In this study, we investigated the impact of RES and SBRT treatment on HCC recurrence and long-term survival in a single institution with the goal of providing evidence that will help surgeons and other practitioners in the treatment and management of patients with HCC.

Methods

Patient selection

Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines were carefully followed in the development of this research. From January 2008 to December 2015, patients who underwent liver resection or SBRT as an initial treatment with curative intent for single or multiple ($\leq$3) HCC measuring $\leq$3 cm at Hiroshima University Hospital, Japan, were included in this retrospective study. Patients who underwent transcatheter arterial chemoembolization (TACE) within 3 months prior to RES or SBRT with no other previous therapies were also included. Diagnosing HCC without biopsy evidence mainly depended on radiological imaging modalities, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and hepatic digital subtraction angiography. The treatment program was decided by the institutional multidisciplinary liver tumor board, which generally followed the Clinical Practice Guidelines for Hepatocellular Carcinoma 2013.[15] This study was approved by the Institutional Review Board and the Ethics Committee of Hiroshima University (Permit Number: E-883) and was conducted in accordance with the 1975 Declaration of Helsinki. All patients provided informed consent.

Hepatic resection

In the current study, 254 patients were treated with RES for early HCC. The indication and procedure for hepatectomy were the same as those described previously.[16,17] Evidence of Child–Pugh class C was one of the exclusion criteria in patient selection. The type of hepatectomy was determined based on liver function and the extent of the tumor. Liver function was assessed using the Child–Pugh classification system and an indocyanine green retention test (ICGR15). For patients without ascites and a normal bilirubin level, eligibility for resectability depended mainly on the ICGR15. Hepatectomy was indicated when preoperative imaging studies, including US, CT, and MRI, showed evidence that hepatic functional reserve would be sufficient postoperatively.

SBRT

In the current study, 27 patients were subjected to SBRT for early HCC. The inclusion criteria for curative SBRT were the same as those described previously[18]: (1) age over 20 years, (2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (3) Child-Turcotte-Pugh class A or B, (4) less than 3 HCC nodules, each up to 50 mm in diameter without portal venous thrombosis or extrahepatic metastases, (5) inoperability because of poor general condition or surgery refusal, and (6) unsuitability for RFA because of tumor location (ie, on the liver surface, which puts a patient at particularly high risk of pneumothorax, and near the porta hepatitis), tumor invisibility on ultrasonography, or bleeding tendencies (platelet count, $\leq 5.0 \times 10^9$ L^{-1}; prothrombin activity, $\leq$50%). The procedure for curative SBRT was also the same as those described previously.[18] In brief, the CT-based 3D conformal method, in which a single high dose was delivered to the tumor, was used. Respiratory motion was coordinated by voluntary breath-holding at the end-inspiratory phase using Abches (APEX Medical, Tokyo, Japan), a device that allows patients to control their chest and abdominal respiratory motion. For simulations, dynamic CT scans (Lightspeed QX/I; GE Medical Systems, Waukesha, WI, USA), including those with non-contrast enhancement, arterial, portal, and venous phases, were obtained by giving a bolus injection of non-ionic iodinated contrast material (100 mL at a rate of 3 mL/s). Arterial phase CT volume data were transferred to a 3-D treatment planning system (Pinnacle3 ver. 9.0; Phillips Medical Systems, Fitchburg, WI, USA). The gross tumor volume (GTV) was defined as the tumor volume containing the remains of iodized oil from TACE and early enhancement in the arterial phase of dynamic CT. The clinical target volume margin was defined as 0 to 5 mm around the GTV. A planning target volume margin of 5 to 8 mm, including the respiratory motion reproducibility and setup error, was added. Eight non-coplanar ports were used in all patients, including a beam direction that avoided critical organs, whenever possible. The prescribed doses and fractionations were evaluated at the isocenter. The SBRT dose and fractionation schedule were selected depending on tumor location. A total dose of 48 Gy in 4 fractions was selected for peripherally located HCC, while 60 Gy in 8 fractions was selected for centrally-located HCC that was located within 5 mm of major vessels, such as the aorta, portal vein, and inferior vena cava.

Follow-up

Follow-up evaluations after RES or SBRT consisted of clinical physical examinations, blood chemistry tests, and measurements of levels of tumor markers, including alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), every month for 2 years and then once every 3 months thereafter. Patients were examined via abdominal ultrasonography every 3 months and via CT or MRI every 6 months during the follow-up periods. The severity of complications was graded according to the Dindo and Clavien classification.[19] The number of cases with Dindo and Clavien classification grade III or higher was documented.

Statistical analyses

All statistical analyses, except propensity score matching, were performed using the JMP software program, version 11 (SAS Institute Inc., Cary, NC, USA). Wilcoxon's rank-sum test was used to compare continuous variables, while the χ^2 test or Fisher's exact probability test was used to compare categorical variables. OS was