Hepatic Resection Versus Stereotactic Body Radiation Therapy Plus Transhepatic Arterial Chemoembolization for Large Hepatocellular Carcinoma: A Propensity Score Analysis

Jing Sun¹, Wen-Gang Li¹, Quan Wang¹, Wei-Ping He¹, Hong-Bo Wang², Ping Han¹, Tao Zhang¹, Ai-Min Zhang¹, Yu-Ze Fan¹, Ying-Zhe Sun¹ and Xue-Zhang Duan¹* ¹

¹Radiation Oncology Department, Fifth Medical Center of Chinese PLA General Hospital, Beijing, China; *Department of Hepatic Surgery, Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Abstract

Background and Aims: There are no comparative studies on the efficacy of hepatic resection (HR) and CyberKnife stereotactic body radiation therapy (CK-SBRT) plus transhepatic arterial chemotherapy embolization (TACE) in the treatment of large hepatocellular carcinoma (HCC). Therefore, this study aimed to compare the efficacy of HR and CK-SBRT+TACE in large HCC. Methods: A total of one hundred and sixteen patients were enrolled in this study from November 2011 to December 2016. Among them, 50 were allocated to the CK-SBRT+TACE group and 66 were allocated to the HR group. The Kaplan-Meier method was calculated to apply overall survival (OS) and progression-free survival (PFS) rates. Propensity score matching was performed to control for baseline differences between the groups. Results: Thirty-six paired patients were selected from the CK-SBRT+TACE and HR groups. After propensity score matching, the 1-, 2- and 3-year OS rates were 83.3%, 77.8% and 66.7% in the HR group and 80.6%, 72.2% and 52.8% in the CK-SBRT+TACE group, respectively. The 1-, 2- and 3-year PFS rates were 71.6%, 57.3% and 42.3% in the HR group and 80.6%, 72.2% and 52.8% in the CK-SBRT+TACE group, respectively. The Kaplan-Meier method was applied to calculate overall survival (OS) and progression-free survival (PFS) rates. Propensity score matching was performed to control for baseline differences between the groups. Results: Thirty-six paired patients were selected from the CK-SBRT+TACE and HR groups. After propensity score matching, the 1-, 2- and 3-year OS rates were 83.3%, 77.8% and 66.7% in the HR group and 80.6%, 72.2% and 52.8% in the CK-SBRT+TACE group, respectively. The 1-, 2- and 3-year PFS rates were 71.6%, 57.3% and 42.3% in the HR group and 80.6%, 72.2% and 52.8% in the CK-SBRT+TACE group, respectively. Both a high platelet count and low alpha-fetoprotein value were revealed as influencing factors in improving OS and PFS. Conclusions: CK-SBRT+TACE brought local effects that were similar to those of HR in HCC patients with a large and single lesion. Moreover, the liver injury occurrence rate was acceptable in both groups.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common cause of cancer-related death.¹ Hepatic resection (HR), radiofrequency ablation (RFA) and liver transplantation (LT) are the main curative methods for HCC, especially for early-stage HCC.² However, without any related syndrome in the early stages of the disease, some HCC patients are at an advanced stage at the time of diagnosis and lose the opportunity for radical treatment. HR and transhepatic arterial chemotherapy embolization (TACE) are widely used for patients with a tumor diameter of 5–10 cm. With the advancement of radiotherapy technologies, CyberKnife stereotactic body radiation therapy (CK-SBRT) has also been applied to patients with large HCC and prolonged their survival, especially among those who were not suitable for or refused other treatments.³,⁴ Previous studies have reported improved outcomes using radiotherapy+TACE combination therapy compared with TACE or radiotherapy alone.⁵,⁶ However, there are no comparative studies on the efficacy of HR and CK-SBRT+TACE in the treatment of large HCC. Therefore, we conducted a retrospective analysis to compare long-term survival following CK-SBRT+TACE versus HR for patients with large HCCs (5–10 cm) that were treated in our medical center.

Methods

The study profile is shown in Figure 1. One hundred and sixteen patients were enrolled in this study from November 2011 to December 2016. Among them, 50 were in the CK-
SBRT+TACE group and 66 were in the HR group.

Eligibility criteria were as follows: 1) HCC patients diagnosed according to an imaging examination, laboratory tests or pathology; 2) a single lesion with a diameter of 5–10 cm; 3) no prior treatment; 4) Child-Pugh classification A or B; 5) no portal vein tumor thrombus on imaging examination; 6) an Eastern Cooperative Oncology Group performance score (commonly referred to as ECOG PS) of 0 or 1; 7) (for patients in the HR group) an indocyanine green retention rate at 15 minutes less than 10%; and 8) (for patients in the CK-SBRT group) normal residual liver volume ≥700 cc and having undergone gastroscopy before treatment.

CK-SBRT procedure

All patients in the CK-SBRT group received fiducial marker implantation before TACE and underwent computed tomography (CT) localization imaging after their liver function recovered. Plain CT scan images were benchmark images, and contrast-enhanced CT or contrast-enhanced magnetic resonance images were used as auxiliary images for fusion. An oncologist contoured the gross tumor volume, planning target volume and organs-at-risk. Planning target volume was defined as 3–5 millimeter expansion of gross tumor volume and avoided organs-at-risk. Prescribed doses were 50–54 Gy/5–6 fx. All plans were calculated by G4 CyberKnife MultiPlan (version 4.0.2) and VSI CyberKnife MultiPlan (version 4.6.1) (Accuracy, USA). Normal tissue tolerance doses were determined according to the AAPM TG-101 report.3

TACE procedure

The patients underwent TACE between fiducial marker implantation and CK-SBRT execution. The femoral artery was accessed via catheterization. Hepatic angiography was performed to observe the common hepatic artery, left and right hepatic arteries, and splenic artery. After localized tumor staining, intervention radiologists inserted a microcatheter into the blood supply vessel and infused it with a mixture of 5–20 mL iodinated oil injection (Lipiodol; Guerbet, Aulnaysous-Bois, France) plus epirubicin (10 mg). If a patient’s tumor had an arteriovenous fistula, gelatin sponge particles (Cutanplast; Mascia Brunelli S.p.A., Milano, Italy) were applied for embolization. After CK-SBRT, the patients received TACE once a month.

HR procedure

Segmental hepatectomy, left hepatectomy and right hepatectomy were applied to remove the tumor. The residual liver volume was estimated from a preoperative volumetric CT scan. Hepatectomy was not executed in patients with a remnant volume less than 30% of the total liver volume, excluding the lesion.4 Intraoperative ultrasound was routinely applied to evaluate the extent of parenchymal resection that could be safely performed. HR could receive R0 resection.

Toxicity reactions and follow-up

Toxicity reactions were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.5 Radiation-induced liver disease (referred to as RILD) was observed among the patients in the CK-SBRT+TACE group.

All patients underwent laboratory tests at least every 3 days during CK-SBRT+TACE/HR treatment. After treatment, the patients were reviewed every 3 months for 1 year and every 6 months thereafter until March 2020 or death.

Statistical analysis

Overall survival (OS) was defined as the period between the beginning of treatment and the final follow-up or death. Progression-free survival (PFS) was defined as the period between the beginning of treatment and the final follow-up or tumor progression. Local control was defined as the pe-
SBRAT+TACE group, as was the proportion of patients with ascites or hydrothorax. Transient liver dysfunction occurred mainly in the HR group and showed mainly a decrease in albumin and an elevation in transaminase. Six patients in the CK-SBRT+TACE group were diagnosed with RILD before PSM, and the details of their liver function before and after CK-SBRT are shown in Table 4.

None of these patients died from the toxicity outcomes and complications of HR or CK-SBRT+TACE. The toxicity reactions and complications in the two groups are shown in Table 5.

Discussion

The treatment of patients with large HCC is a considerable challenge. Some studies reported that ablation or HR therapy could achieve certain efficacy. Xu et al.7 reported the outcomes of patients with 5–6 cm unresectable HCCs who received microwave ablation. They found that the 1-, 3- and 5-year OS rates were 92.7%, 63.4% and 41.1%, respectively, and the corresponding recurrence-free survival rates were 65.9%, 31.7% and 23.0%, respectively. Although the tumor size was smaller in their study than in ours, their 3-year OS rate was similar to ours, and the 3-year recurrence-free survival rates were lower than our PFS rates. Zhao et al.8 conducted a retrospective analysis of patients with large HCC undergoing HR. Ninety-nine patients were enrolled in their study. Two patients died of hepatic failure within 30 days after surgery. The 1-, 3- and 5-year disease-free survival and OS rates following HR were 67% and 49% and 37% and 77%, 56%, and 43%, respectively. Hsu et al.9 evaluated the long-term outcomes after HR in elderly patients with resectable large HCC compared with those in younger patients. The 1-, 3-, 5- and 7-year OS rates in the elderly/younger groups were 76%/79%, 55%/57%, 48%/51% and 42%/49%, respectively. The 1-, 3-, 5- and 7-year disease-free survival rates in the elderly/younger groups were 60%/54%, 40%/36%, 38%/32%, and 27%/32%, respectively. The OS rate in our study was higher than that in theirs. We believe that this finding may be related to the fact that all patients in the HR group of our study were of Child-Pugh A classification and with single lesion, both of which are influencing factors for improving prognosis. SBRAT has been applied in the HCC treatment field for over 20 years9 and has achieved a satisfactory effect on HCC patients, and the number of related studies published in recent years has increased. To date, there have been more studies on patients with small HCC10-12 than on patients with large HCC. Shibata et al.13 applied proton beam therapy to patients with large HCC, in which the tumor size ranged from 5.0 to 13.9 cm. Twenty-four patients were classified as Child-Pugh A, and five patients were classified as Child-Pugh B. The 2-year Local control (LC), PFS and OS rates were 95%, 22% and 61%, respectively. Beaton et al.14 described 13 patients with large HCC whose median tumor size ranged from 5.1 to 9.7 cm and were treated with SBRT. The prescribed doses were 40–45 Gy in five fractions. They reported a median OS of 17.7 months and a 1-year OS rate of 62%. SBRT provides an effective treatment for patients with large HCC, especially for patients who are not suitable for or unwilling to receive other treatments.

The AFP value and PLT count were significant factors of OS and PFS in our study. A similar AFP value was reported in previous studies.16,17 The PLT count could serve as an indicator for the degree of cirrhosis by indicating the degree of hypersplenism and portal hypertension,17 and complications of cirrhosis were the main cause of death. Moreover,
Table 1. Characteristics of patients before and after PSM in this study

| Patients details                  | Before PSM | std. mean diff | After PSM | std. mean diff |
|----------------------------------|------------|----------------|-----------|----------------|
| **Total enrolled patients**      |            |                |           |                |
| Number of patients               | 116        | 66             | 50        | 36             |
| **Sex**                          |            |                |           |                |
| Male                             | 97 (83.6)  | 56 (84.8)      | 41 (82.0) | 30 (83.3)      |
| Female                           | 19 (16.4)  | 10 (15.2)      | 9 (18.0)  | 6 (16.7)       |
| **Age in years**                 | 54.1±10.27 | 52.52±8.98     | 56.2±11.51| 53.72±8.66     |
| **Diameter of tumor in cm**      | 6.74±1.34  | 6.93±1.27      | 6.49±1.41 | 6.73±1.19      |
| **Type of chronic hepatitis**    |            |                |           |                |
| Hepatitis B virus infection      | 101 (87.1)| 58 (87.9)      | 43 (86.0) | 32 (88.9)      |
| Hepatitis C virus infection      | 5 (4.3)    | 1 (1.5)        | 4 (8.0)   | 1 (2.8)        |
| Without hepatitis virus infection| 10 (8.6)  | 7 (10.6)       | 3 (6.0)   | 3 (8.3)        |
| **Child-Pugh classification**    |            |                |           |                |
| CP-A                             | 112 (96.6)| 66 (100.0)     | 46 (92.0) | 36 (100.0)     |
| CP-B                             | 4 (3.4)    | 0 (0.0)        | 4 (8.0)   | 0 (0.0)        |
| **Alpha fetoprotein value in ng/mL** |      |                |           |                |
| <200                             | 84 (72.4) | 53 (80.3)      | 31 (62.0) | 23 (63.9)      |
| ≥200                             | 32 (27.6) | 13 (19.7)      | 19 (38.0) | 12 (33.3)      |
| **ECOG PS score**                |            |                |           |                |
| 0                                | 77 (66.4) | 45 (68.2)      | 32 (64.0) | 22 (61.1)      |
| 1                                | 39 (33.6) | 21 (31.8)      | 18 (36.0) | 14 (38.9)      |
| **White blood count as ×10⁹/L**  | 5.46±1.80 | 5.26±1.85      | 5.61±1.75 | 5.59±2.01      |
| **Platelet count as ×10⁹/L**     | 159.60±68.74 | 176.47±66.78 | 137.34±65.46 | 154.64±58.79 |
### Table 2. Recurrence, metastases, treatment and cause of death of patients before and after PSM in this study

| Patients details                  | Before PSM | After PSM | p    | Before PSM | After PSM | p    |
|----------------------------------|------------|-----------|------|------------|-----------|------|
|                                  | HR group   | CK-SBRT+TACE group | p    | HR group   | CK-SBRT+TACE group | p    |
| Number of patients with metastases | 44         | 31        | 0.603 | 24         | 24        | 1.000 |
| Single organ metastasis          |            |           |       |            |           |      |
| Liver                            | 40 (90.9)  | 29 (93.5) |       | 21         | 21 (87.5) |       |
| Lung                             | 35 (79.5)  | 22 (71.0) |       | 19         | 19 (79.2) |       |
| Lymph node                       | 0 (0.0)    | 2 (6.5)   |       | 0 (0.0)    | 0 (0.0)   |       |
| Bone                             | 2 (4.6)    | 2 (6.5)   |       | 0 (0.0)    | 1 (4.2)   |       |
| Adrenal gland                    | 1 (2.3)    | 0 (0.0)   |       | 0 (0.0)    | 0 (0.0)   |       |
| Multiple organ metastasis        | 4 (9.1)    | 2 (6.5)   |       | 3 (12.5)   | 3 (12.5)  |       |
| Subsequent therapy               |            |           |       |            |           |      |
| Single treatment                 | 29 (65.9)  | 15 (48.4) |       | 15         | 12 (50.0) |       |
| Hepatic resection                | 2 (4.6)    | 0 (0.0)   |       | 1 (4.2)    | 0 (0.0)   |       |
| Trans-arterial chemoembolization | 14 (31.8)  | 0 (0.0)   |       | 4 (16.7)   | 0 (0.0)   |       |
| Radio-frequency ablation         | 7 (15.9)   | 0 (0.0)   |       | 5 (20.8)   | 0 (0.0)   |       |
| CK-SBRT                          | 5 (11.4)   | 14 (45.2) |       | 4 (16.7)   | 11 (45.8) |       |
| Target therapy or immunotherapy  | 1 (2.3)    | 1 (3.2)   |       | 1 (4.2)    | 1 (4.2)   |       |
| Multiple treatments              | 4 (9.1)    | 1 (3.2)   |       | 1 (4.2)    | 1 (4.2)   |       |
| Conservative treatment           | 11 (25.0)  | 15 (48.4) |       | 8 (33.3)   | 11 (45.8) |       |
| Number of dead patients          | 31         | 29        | 0.239 | 16         | 22        | 0.157 |
| Cause of death                   |            |           |       |            |           |      |
| Liver failure                    | 12 (38.7)  | 10 (34.5) |       | 4 (25.0)   | 8 (36.4)  |       |
| Upper gastrointestinal hemorrhage| 5 (16.1)   | 6 (20.7)  |       | 3 (18.8)   | 5 (22.7)  |       |
| Infectious shock                 | 8 (25.8)   | 1 (3.4)   |       | 6 (37.5)   | 0 (0.0)   |       |
| Other causes                     | 1 (3.2)    | 5 (17.2)  |       | 1 (6.2)    | 3 (13.6)  |       |
| Unknown                          | 5 (16.1)   | 7 (24.1)  |       | 2 (12.5)   | 6 (27.3)  |       |

CK-SBRT, CyberKnife stereotactic body radiation therapy; HR, hepatic resection; PSM, propensity score matched analysis; TACE, transhepatic arterial chemoembolization.
an adequate PLT count was one of the necessary conditions for treatment of relapse.

This study is the first to compare the efficacy and complications of SBRT+TACE and HR in patients with large HCC. The main adverse reactions in the SBRT group were nausea and vomiting, which were mainly related to exposure of the gastrointestinal tract to radiation during therapy. We found that RILD occurred only in six patients, and there were no deaths. Compared to conventional radiation therapy, CK-SBRT improved accuracy through noncoplanar irradiation and better protected normal residual liver function by adopting fiducial marker tracking combined with dynamic respiration tracking. Fatigue and abdominal pain were the main syndromes in the HR group, and some patients had ascites or hydrothorax, which was mainly related to surgical trauma, and most patients recovered within 3 weeks. Although the OS curve of HR seems to be higher than that of CK, the difference in OS between the two groups was not statistically significant before and after PSM. After relapse or metastases, patients in the HR group received more types of follow-up treatment, and the proportion of patients who received multiple treatments was higher than that of those who received CK-SBRT+TACE. However, the majority of patients in the CK-SBRT+TACE group received repeated CK-SBRT only. Moreover, the proportion of patients in the CK-SBRT+TACE group who received conservative therapy was higher than that in the HR group. Although the choice of treatment was related to the patients, it may have affected the prognosis.

TACE has been widely applied to patients with large HCC in clinical practice. Jin et al. compared the OS outcomes of patients with large HCC and a single tumor treated with HR and TACE. In their study, 206 patients were in the HR group, and 489 patients were in the TACE group. The cumulative OS rates at 1, 3 and 5 years in the HR group were significantly higher than those in the TACE group. Previous studies showed that CK-SBRT combined with TACE could prolong survival in patients with nonresectable HCC. Wong et al. conducted a retrospective study of two centers in Hong Kong. After PSM, 49 patients were in the TACE+SBRT group, and 98 patients were in the TACE alone group. The 1- and 3-year OS rates in the TACE+SBRT group and TACE alone group were 67.2% versus 43.9% and 36.5% versus 13.3%, respectively. The 1- and 3-year PFS rates in the TACE + SBRT group and TACE alone group were 32.5% versus 21.4% and 15.1% versus 5.1%, respectively. Su et al. described 77 patients who received SBRT followed by transcatheter arterial embolization (commonly known as TAE).
Table 3. Univariate and multivariate Cox hazard analyses of risk factors for OS and PFS in all patients enrolled in this study

| Patients details                          | OS Univariate Cox regression | OS Multivariate Cox regression | PFS Univariate Cox regression | PFS Multivariate Cox regression |
|------------------------------------------|------------------------------|--------------------------------|-------------------------------|---------------------------------|
|                                          | p value | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) |
| Sex                                      |         |                      |         |                      |         |                      |         |                      |
| Male versus female                       | 0.983   | 1.007 (0.510–1.988) | 0.739   | 1.134 (0.541–2.377) | 0.450   | 1.293 (0.664–2.520)  | 0.361   | 1.409 (0.676–2.939)  |
| Age in years                             | 0.613   | 1.007 (0.510–1.988) | 0.162   | 0.981 (0.955–1.008) | 0.445   | 0.992 (0.971–1.013)  | 0.217   | 0.985 (0.962–1.009)  |
| Diameter of tumor in cm                  | 0.506   | 1.067 (0.881–1.293) | 0.235   | 1.134 (0.921–1.395) | 0.345   | 1.091 (0.911–1.307)  | 0.268   | 1.114 (0.920–1.347)  |
| Type of chronic hepatitis                |         |                      |         |                      |         |                      |         |                      |
| B versus C versus none                   | 0.614   | 0.907 (0.621–1.326) | 0.078   | 0.650 (0.402–1.050) | 0.693   | 0.932 (0.657–1.323)  | 0.245   | 0.778 (0.509–1.189)  |
| Child-Pugh classification                |         |                      |         |                      |         |                      |         |                      |
| CP-A versus CP-B                         | 0.048   | 2.354 (1.006–5.505) | 0.066   | 2.353 (0.947–5.851) | 0.581   | 1.327 (0.486–3.625)  | 0.518   | 1.424 (0.488–4.155)  |
| Alpha fetoprotein value in ng/mL         |         |                      |         |                      |         |                      |         |                      |
| <200 versus ≥200                         | 0.093   | 1.559 (0.928–2.618) | 0.025   | 1.842 (1.079–3.147) | 0.086   | 1.522 (0.942–2.458)  | 0.025   | 1.765 (1.073–2.902)  |
| ECOG PS                                  |         |                      |         |                      |         |                      |         |                      |
| 0 versus 1                               | 0.797   | 0.935 (0.560–1.560) | 0.832   | 1.062 (0.611–1.846) | 0.755   | 1.076 (0.680–1.702)  | 0.579   | 1.154 (0.696–1.911)  |
| White blood count as $\times 10^9$/L    | 0.671   | 0.967 (0.830–1.127) | 0.504   | 1.069 (0.879–1.299) | 0.395   | 1.058 (0.929–1.204)  | 0.259   | 1.103 (0.930–1.307)  |
| Platelet count as $\times 10^9$/L        | 0.080   | 0.997 (0.993–1.000) | 0.008   | 0.992 (0.987–0.998) | 0.569   | 1.327 (0.486–3.625)  | 0.045   | 0.995 (0.990–1.000)  |

ECOG PS, Eastern Cooperative Oncology Group performance score; OS, overall survival rates; PFS, progression-free survival rates.
Sun J. et al: HR VS. SBRT plus TACE for Large HCC

or TACE and 50 patients who received SBRT alone. The 1-, 3- and 5-year OS rates were 75.5%, 50.8% and 46.9% in the TAE/TACE+SBRT group and 62.4%, 32.9% and 32.9% in the SBRT group, respectively. All their results showed that SBRT combined with TACE could better improve survival than SBRT or TACE alone. We conjectured that SBRT may normalize the tumor vasculature and increase embolization rates and that TACE/TAE could eliminate subclinical lesions, which prolonged PFS and OS.

It is difficult to carry out a prospective randomized controlled cohort study to compare the efficacy of CK-SBRT+TACE and HR in treating patients with large HCC. However, based on our results, we believe that CK-SBRT combined with TACE could offer a strategy for improving the survival of patients with large HCC, especially those who were not suitable for HR.

**Conclusions**

Our results showed that CK-SBRT+TACE and HR provide similar OS and PFS benefits for patients with large HCC. CK-SBRT+TACE could offer a treatment option for patients with large HCC who are not suitable for or refuse other treatments. The toxicity reactions and complications in the two groups were acceptable.

**Table 4. Details of patients who were diagnosed with RILD before and after CK-SBRT**

| ALP | Bilirubin | ALT | AST | ALB | Ascites |
|-----|-----------|-----|-----|-----|---------|
| Pre- | Post- | Pre- | Post- | Pre- | Post- | Pre- | Post- | Pre- | Post- |
| Classic RILD |
| 80 | 245 | 17.1 | 20.1 | 34 | 33 | 36 | 36 | 43 | 35 | – | + |
| Non-classic RILD |
| 98 | 112 | 12.4 | 32.1 | 33 | 424 | 32 | 286 | 38 | 32 | – | + |
| 98 | 121 | 20.1 | 51.7 | 40 | 34 | 42 | 114 | 35 | 33 | – | + |
| 67 | 136 | 22.7 | 55.6 | 30 | 608 | 28 | 363 | 36 | 40 | – | – |
| 165 | 144 | 26.9 | 43.8 | 19 | 68 | 40 | 75 | 31 | 28 | – | + |
| 79 | 81 | 18.5 | 35.6 | 28 | 17 | 37 | 42 | 39 | 34 | – | – |

ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CK-SBRT, CyberKnife Stereotactic body radiation therapy; RILD, radiation induced liver injury.
Table 5. Toxicity reaction and complications of patients before and after PSM in this study

| Adverse reaction                              | Before PSM                                      | After PSM                                      | p     |
|-----------------------------------------------|------------------------------------------------|------------------------------------------------|-------|
|                                               | HR group | CK-SBRT+TACE group | p     | HR group | CK-SBRT+TACE group | p     |
| Number of patients                            | 66       | 50                  | 0.000 | 36       | 36                  | 0.064 | 0.077 |
| Nausea/vomiting                               |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 0 (0.0)  | 28 (56.0)           | 0.000 | 0 (0.0)  | 5 (13.9)            | 0.000 |       |
| Anorexia                                       |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 22 (33.3)| 32 (64.0)           | 0.001 | 8 (22.2) | 15 (41.7)           | 0.001 | 0.077 |
| Fatigue                                        |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 17 (25.8)| 16 (32.0)           | 0.461 | 11 (30.6)| 7 (19.4)            | 0.276 |       |
| Grade ≥3                                      | 6 (9.1)  | 0 (0.0)             | 0.077 | 2 (5.7)  | 0 (0.0)             | 0.473 |       |
| Abdominal pain                                 |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 32 (48.5)| 5 (10.0)            | 0.000 | 15 (41.7)| 4 (11.1)            | 0.007 |       |
| Grade ≥3                                      | 7 (10.6) | 0 (0.0)             | 0.047 | 2 (5.7)  | 0 (0.0)             | 0.473 |       |
| Anemia                                         |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 15 (22.7)| 3 (6.0)             | 0.027 | 6 (16.7) | 0 (0.0)             | 0.033 |       |
| Grade ≥3                                      | 2 (3.0)  | 0 (0.0)             | 0.602 | 0 (0.0)  | 0 (0.0)             | 1.000 |       |
| Ascites                                        |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 15 (22.7)| 4 (8.0)             | 0.062 | 8 (22.2) | 2 (5.6)             | 0.088 |       |
| Hydrothorax                                    |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 5 (75.8)| 0 (0.0)             | 0.127 | 1 (2.8)  | 0 (0.0)             | 1.000 |       |
| ALT increase                                   |          |                     |       |          |                     |       |       |
| Grade 1–2                                     | 33 (50.0)| 10 (20.0)           | 0.001 | 15 (41.7)| 7 (19.4)            | 0.041 |       |
| Grade ≥3                                      | 18 (27.3)| 2 (4.0)             | 0.002 | 5 (13.9) | 0 (0.0)             | 0.064 |       |
| Child-Pugh score increasing by two points (one of the RILD criteria) | 19 (28.8)| 5 (10.0)           | 0.013 | 10 (27.8)| 3 (8.3)             | 0.066 |       |
| Patients with RILD                             | –        | 6 (12.0)            |       | –        | 3 (8.3)             |       |       |

ALT, alanine aminotransferase; CK-SBRT, CyberKnife stereotactic body radiation therapy; HR, hepatic resection; PSM, propensity score matched analysis; RILD, radiation-induced liver disease; TACE, transhepatic arterial chemoembolization.

Funding

This study protocol was supported by a grant from the Beijing Municipal Science and Technology Commission Fund (Z171100001017181).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Data analysis and interpretation, and drafting and revision of the manuscript for critically important intellectual content (JS, WGL, QW), data acquisition (HBW, TZ, YZF), manuscript preparation (WPH, AMZ, PH, YZS), and provision of final approval of the version to be published (XZD). All authors have read and approved the final version.

Ethics statement

This study was approved by the Institutional Review Board of Beijing 302 Hospital and was conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines. All patients signed written informed consent for their information to be stored in the hospital databases and used for research.

Data sharing statement

All data are available upon request.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424. doi:10.3322/caac.21492.
[2] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 2018;68(2):723–750. doi:10.1002/hep.29913.
[3] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37(8):4078–4101. doi:10.1118/1.3438081.
[4] Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 2005;12(1):16–22. doi:10.1007/s00534-004-0965-9.
[5] Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC, et al. Grading dermatologic adverse events of cancer treatments: the common
terminology criteria for adverse events version 4.0. J Am Acad Dermatol 2012;67(5):1025–1039. doi:10.1016/j.jaad.2012.02.010.

[6] Xu Y, Shen Q, Wang N, Liu P, Wu P, Peng Z, et al. Percutaneous microwave ablation of 5–6 cm unresectable hepatocellular carcinoma: local efficacy and long-term outcomes. Int J Hyperthermia 2017;33(3):247–254. doi:10.1080/02656736.2016.1239842.

[7] Zhao HC, Wu RL, Liu FB, Zhao YJ, Wang GB, Zhang ZG, et al. A retrospective analysis of long term outcomes in patients undergoing hepatic resection for large (>5 cm) hepatocellular carcinoma. HPB (Oxford) 2016;18(11):943–949. doi:10.1016/j.hpb.2016.08.005.

[8] Hsu KF, Yu JC, Yang CW, Chen BC, Chen CJ, Chan DC, et al. Long-term outcomes in elderly patients with resectable large hepatocellular carcinoma undergoing hepatectomy. Surg Oncol 2018;27(3):595–601. doi:10.1016/j.suronc.2018.07.009.

[9] Blomgren H, Lax I, Näslund I, Svanström R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34(6):861–870. doi:10.3109/02841869509127197.

[10] Zhang T, Sun J, He W, Li H, Piao J, Xu H, et al. Stereotactic body radiation therapy as an effective and safe treatment for small hepatocellular carcinoma. BMC Cancer 2018;18(1):451. doi:10.1186/s12885-018-4359-9.

[11] Su TS, Liang P, Lu HZ, Liang J, Gao YC, Zhou Y, et al. Stereotactic body radiation therapy for small primary or recurrent hepatocellular carcinoma in 132 Chinese patients. J Surg Oncol 2016;113(2):181–187. doi:10.1002/jso.24129.

[12] Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol 2016;34(5):452–429. doi:10.1200/JCO.2015.61.4925.

[13] Shibata S, Takamatsu S, Yamamoto K, Mizuhata M, Bou S, Sato Y, et al. Proton beam therapy without fiducial markers using four-dimensional CT planning for large hepatocellular carcinomas. Cancers (Basel) 2018;10(3):71. doi:10.3390/cancers10030071.

[14] Beaton L, Dunne EM, Yeung R, Rackley T, Weber B, Mar C, et al. Stereotactic body radiotherapy for large unresectable hepatocellular carcinomas - a single institution phase II study. Clin Oncol (R Coll Radiol) 2020;32(7):423–432. doi:10.1016/j.clon.2020.01.028.

[15] Huo L, Wei W, Yan Z, Li Z, Xie Y, Gong K, et al. Short-term and long-term outcomes of liver resection for HCC patients with portal vein tumor thrombus. Cell Biosci 2019;9:23. doi:10.1186/s13578-019-0285-z.

[16] Mehta N, Dodge JL, Roberts JP, Hirose R, Yao FY. Alpha-fetoprotein decrease from > 1,000 to < 500 ng/mL in patients with hepatocellular carcinoma leads to improved posttransplant outcomes. Hepatology 2019;69(3):1193–1205. doi:10.1002/hep.30413.

[17] Wang L, Feng Y, Ma X, Wang G, Wu H, Xie X, et al. Diagnostic efficacy of noninvasive liver fibrosis indexes in predicting portal hypertension in patients with cirrhosis. PLoS One 2017;12(8):e0182969. doi:10.1371/journal.pone.0182969.

[18] Jin YJ, Lee JW. Therapeutic priorities for solitary large hepatocellular carcinoma in a hepatitis B virus endemic area; an analysis of a nationwide cancer registry database. J Surg Oncol 2017;115(4):407–416. doi:10.1002/jso.24519.

[19] Wong TC, Chiang CL, Lee AS, Lee VH, Yeung CS, Ho CH, et al. Better survival after stereotactic body radiation therapy following transarterial chemoembolization in nonresectable hepatocellular carcinoma: a propensity score matched analysis. Surg Oncol 2019;28:228–235. doi:10.1016/j.suronc.2019.01.006.

[20] Su TS, Lu HZ, Cheng T, Zhou Y, Huang Y, Gao YC, et al. Long-term survival analysis in combined transarterial embolization and stereotactic body radiation therapy versus stereotactic body radiation monotherapy for unresectable hepatocellular carcinoma >5 cm. BMC Cancer 2016;16(1):834. doi:10.1186/s12885-016-2894-9.