



Original Article

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

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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 selected 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 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 66.1%, 45.8% and 39.3% in the CK-SBRT+TACE group, respectively (OS: $p=0.143$; PFS: $p=0.445$). 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.

Keywords: CyberKnife; Radiation-induced liver disease; Survival rates; Large hepatocellular carcinoma.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-SBRT, CyberKnife stereotactic body radiation therapy; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance score; HCC, hepatocellular carcinoma; HR, hepatic resection; LC, Local control; LT, liver transplantation; MRI, Magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PLT, platelet; PSM, propensity score matched analysis; RFA, radiofrequency ablation; RILD, radiation-induced liver disease; TACE, transhepatic arterial chemoembolization; TAE, transcatheter arterial embolization.

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Moreover, the liver injury occurrence rate was acceptable in both groups.

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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.^{5–7} 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-

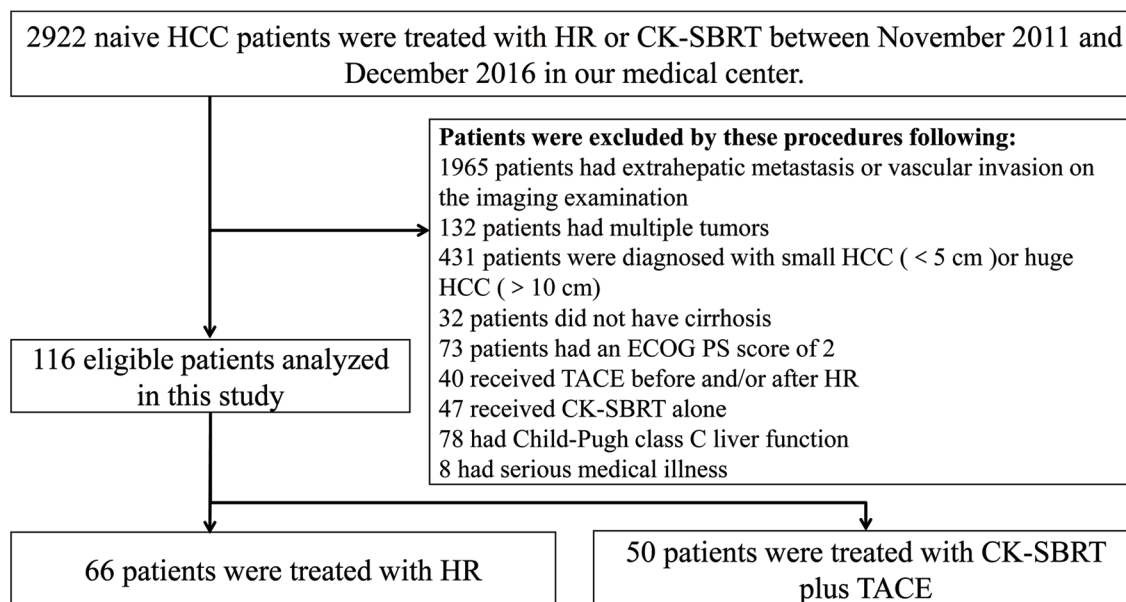


Fig. 1. Flow diagram showing the screening, enrollment, and treatment allocation of patients.

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, Aulnay-sous-Bois, France) plus epirubicin (10 mg). If a patient's tumor had an arteriovenous fistula, gelatin sponge particles (Cutanplast; Mascia Bruneili 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-

riod between the beginning of treatment to the progression of the previously treated lesion or the final follow-up. Propensity score matching (PSM) at a 1:1 ratio was performed to balance the CK-SBRT+TACE and HR patient cohorts. The Kaplan-Meier method was applied to calculate survival rates. The log-rank test was used to compare survival outcomes of the two groups. The χ^2 test or Fisher's exact test was used to compare baseline variables of the two groups. All statistical analyses were performed using STATA (version 15.0; STATA Corp., College Station, TX, USA) and SPSS (version 23.0; IBM Corp., NY, Armonk, USA). A p -value of < 0.05 was considered statistically significant.

Results

The patients' characteristics are shown in Table 1. The proportions of patients with an alpha-fetoprotein (AFP) value ≥ 200 ng/mL or a low platelet (PLT) count were higher in the CK-SBRT+TACE group than in the HR group. After PSM, 36 paired patients were selected from the two groups, and no significant differences in variables were observed.

Recurrence/metastasis, subsequent treatment and cause of death

By March 2020, 75 patients had developed relapse or metastasis (44 patients in the HR group and 31 patients in the CK-SBRT+TACE group), and 60 patients had died (31 patients in the HR group and 29 patients in the CK-SBRT+TACE group). After PSM, 48 patients had developed recurrence or metastasis (24 patients in the HR group and 24 patients in the CK-SBRT+TACE group), and 38 patients had died (16 patients in the HR group and 22 patients in the CK-SBRT+TACE group). The details are shown in Table 2.

Survival analyses

Before PSM, the 1-, 2- and 3-year OS rates were 80.0%, 70.0% and 54.0% in the CK-SBRT+TACE group and 83.3%, 71.2% and 63.6% in the HR group, respectively ($p=0.213$; Fig. 2A). The 1-, 2- and 3-year PFS rates were 65.4%, 46.2% and 41.6% in the CK-SBRT+TACE group and 63.1%, 49.3% and 41.4% in the HR group, respectively ($p=0.923$; Fig. 2B). After PSM, 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 ($p=0.143$; Fig. 2C). The 1-, 2- and 3-year PFS rates were 71.6%, 57.3% and 42.3% in the HR group and 66.1%, 45.8% and 39.3% in the CK-SBRT+TACE group, respectively ($p=0.445$; Fig. 2D). There was no significant difference in OS and PFS. The influencing factors of OS and PFS are shown in Table 3, and we found that a low AFP value and high PLT count were influencing factors in improving OS and PFS for all patients with large HCC.

Two patients are shown in the figures, including one who received CK-SBRT+TACE (Fig. 3A–C) and one who received HR (Fig. 3D–F).

Toxicity reactions and complications

The main common adverse reactions in the two groups were grade 1–2 gastrointestinal reactions, including nausea, vomiting and anorexia. No grade ≥ 3 gastrointestinal toxicities were observed. The proportion of patients with abdominal pain in the HR group was higher than that in the CK-

SBRT+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.*⁶ 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.*⁷ 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.*⁸ 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.

SBRT 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 HCC^{10–12} 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.^{15,16} 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				After PSM				
	Total enrolled patients	HR group	CK-SBRT+ TACE group	P	Std. mean diff	HR group	CK-SBRT+ TACE group	P	Std. mean diff
Number of patients	116	66	50			36	36		
Sex									
Male	97 (83.6)	56 (84.8)	41 (82.0)	0.681	0.079	30 (83.3)	29 (80.6)	0.759	-0.077
Female	19 (16.4)	10 (15.2)	9 (18.0)	0.681	0.079	6 (16.7)	7 (19.4)	0.759	-0.077
Age in years	54.1±10.27	52.52±8.98	56.2±11.51	0.055	-0.410	53.72±8.66	53.5±10.92	0.943	0.019
Diameter of tumor in cm	6.74±1.34	6.93±1.27	6.49±1.41	0.079	0.349	6.73±1.19	6.74±1.51	0.978	-0.007
Type of chronic hepatitis									
Hepatitis B virus infection	101 (87.1)	58 (87.9)	43 (86.0)	0.174	0.109	32 (88.9)	32 (88.9)	1.000	0.000
Hepatitis C virus infection	5 (4.3)	1 (1.5)	4 (8.0)	0.174	-0.527	1 (2.8)	1 (2.8)	1.000	0.000
Without hepatitis virus infection	10 (8.6)	7 (10.6)	3 (6.0)	0.174	-	3 (8.3)	3 (8.3)	1.000	-
Child-Pugh classification									
CP-A	112 (96.6)	66 (100.0)	46 (92.0)	0.009	-	36 (100.0)	36 (100.0)	1.000	-
CP-B	4 (3.4)	0 (0.0)	4 (8.0)	0.009	-	0 (0.0)	0 (0.0)	1.000	-
Alpha fetoprotein value in ng/mL									
<200	84 (72.4)	53 (80.3)	31 (62.0)	0.029	-0.132	23 (63.9)	24 (66.7)	0.804	-0.059
≥200	32 (27.6)	13 (19.7)	19 (38.0)	0.029	-0.132	13 (36.1)	12 (33.3)	0.804	-0.059
ECOG PS score									
0	77 (66.4)	45 (68.2)	32 (64.0)	0.637	0.001	22 (61.1)	21 (58.3)	0.810	-0.056
1	39 (33.6)	21 (31.8)	18 (36.0)	0.637	-0.001	14 (38.9)	15 (41.7)	0.810	0.056
White blood count as ×10 ⁹ /L	5.46±1.80	5.26±1.85	5.61±1.75	0.307	0.197	5.59±2.01	5.41±1.80	0.688	0.103
Platelet count as ×10 ⁹ /L	159.60±68.74	176.47±66.78	137.34±65.46	0.002	0.586	154.64±58.79	150.78±66.15	0.794	0.058

CK-SBRT, CyberKnife stereotactic body radiation therapy; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hepatic resection; PSM, propensity score matched analysis; TACE, transhepatic arterial chemoembolization.

Table 2. Recurrence, metastases, treatment and cause of death of patients before and after PSM in this study

Patients details	Before PSM			After PSM		
	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	40 (90.9)	29 (93.5)		21 (87.5)	21 (87.5)	
Liver	35 (79.5)	22 (71.0)		19 (79.2)	19 (79.2)	
Lung	3 (6.8)	3 (9.7)		2 (8.3)	1 (4.2)	
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 (62.5)	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)	
(Target therapy)		(Immunotherapy)		(Target therapy)	(Immunotherapy)	
Multiple treatments	4 (9.1)	1 (3.2)		1 (4.2)	1 (4.2)	
(SBRT+RFA)						
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.

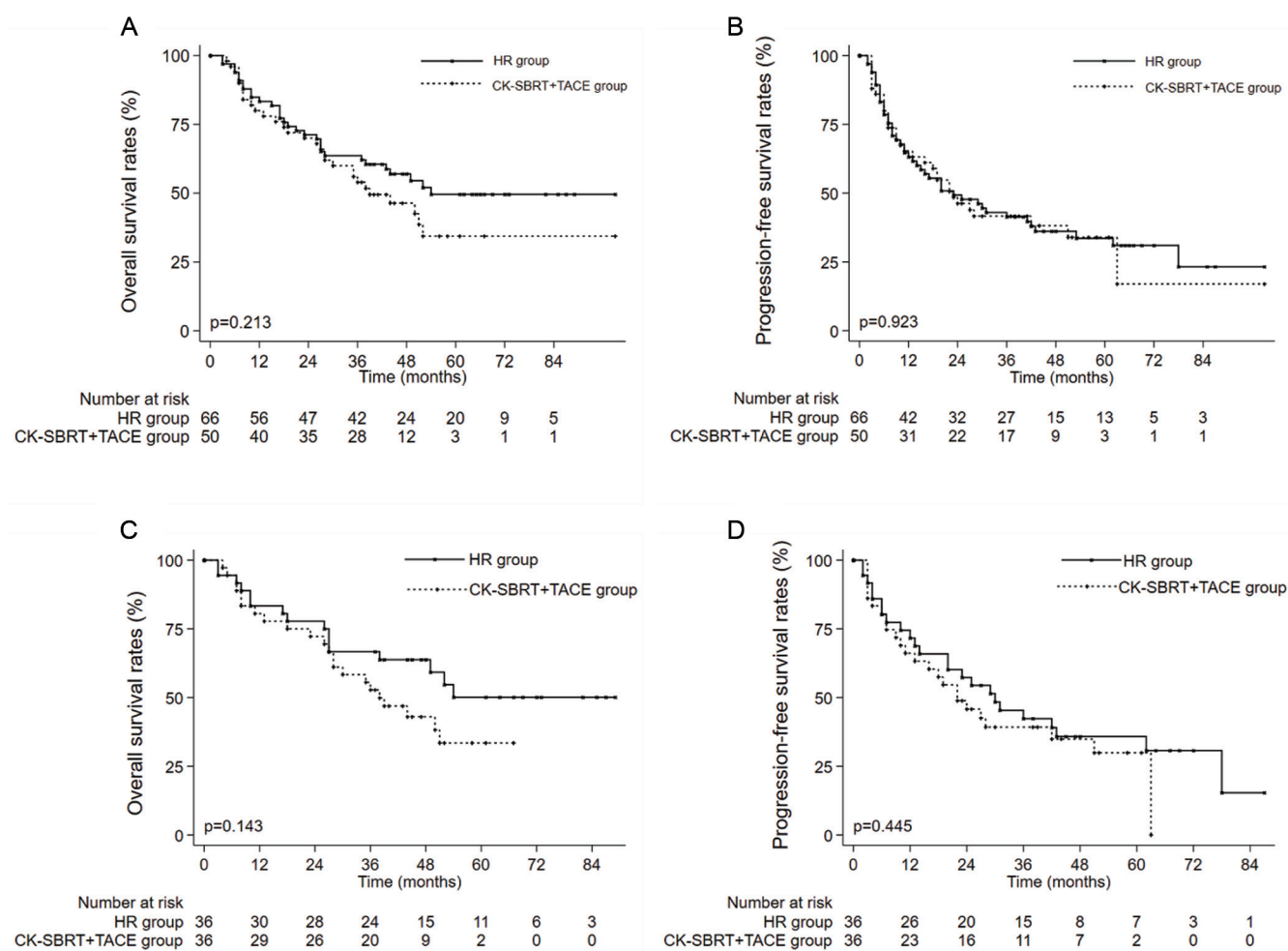


Fig. 2. Comparison of the groups who received CK-SBRT+TACE and HR group. (A) OS rates ($p=0.213$). (B) PFS rates ($p=0.923$). (C–D) Following PSM, OS rates (C) ($p=0.143$) and PFS rates (D) ($p=0.445$). CK-SBRT, CyberKnife stereotactic body radiation therapy; HR, hepatic resection; TACE, transhepatic 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.*¹⁸ 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.*¹⁹ 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.*²⁰ 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						PFS						
	Univariate Cox regression			Multivariate Cox regression			Univariate Cox regression			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)	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 ×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 ×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.

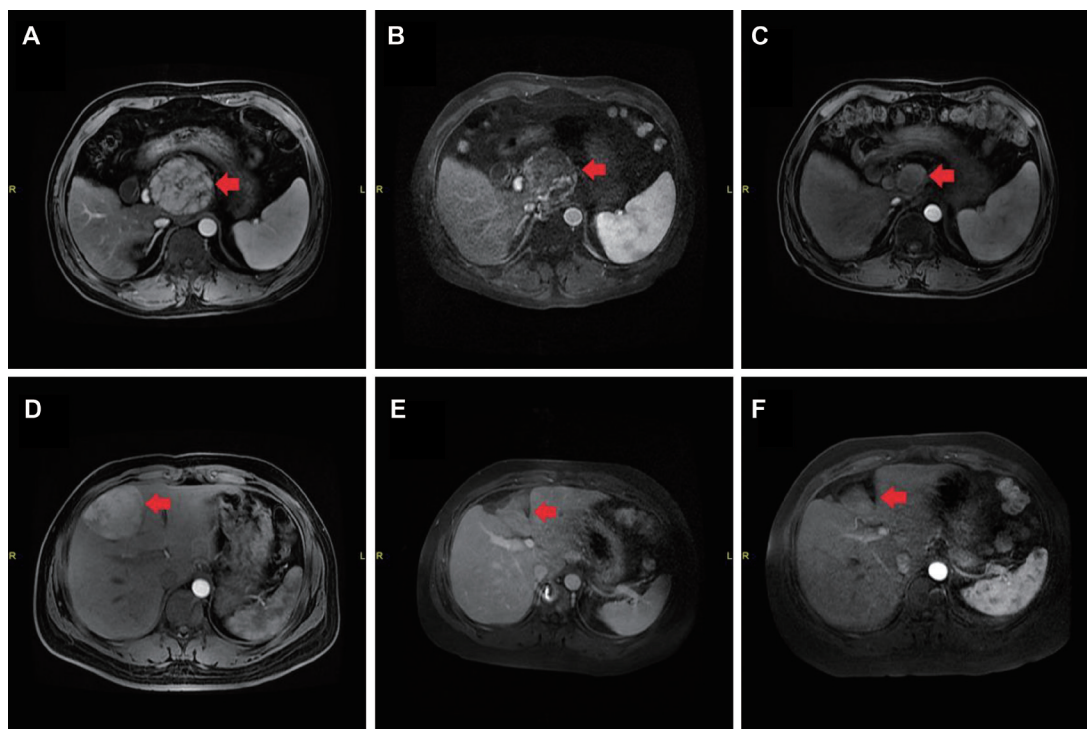


Fig. 3. Magnetic resonance imaging (MRI) of patients with large HCC who were treated with CK-SBRT+TACE and HR. (A–C) are for a patient treated with CK-SBRT+TACE, primary abdominal scan showing the HCC lesion (A), at 6 months after CK-SBRT+TACE (B), and at 2 years after CK-SBRT+TACE (C). (D–F) are for a patient treated with HR, primary abdominal MRI scan showing the HCC lesion (D), at 6 months after HR (E), and at 2 years after HR (F). CK-SBRT, CyberKnife stereotactic body radiation therapy; HCC, hepatocellular carcinoma; HR, hepatic resection; MRI, Magnetic resonance imaging; TACE, transhepatic arterial chemoembolization.

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-	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		
	HR group	CK-SBRT+TACE group	<i>p</i>	HR group	CK-SBRT+TACE group	<i>p</i>
Number of patients	66	50		36	36	
Nausea/vomiting						
Grade 1–2	0 (0.0)	28 (56.0)	0.000	0 (0.0)	5 (13.9)	0.064
Anorexia						
Grade 1–2	22 (33.3)	32 (64.0)	0.001	8 (22.2)	15 (41.7)	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	15 (22.7)	4 (8.0)	0.062	8 (22.2)	2 (5.6)	0.088
Hydrothorax	5 (7.5)	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.

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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.

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